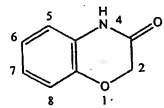
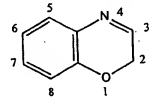
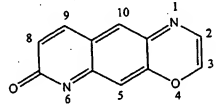
A 2*H*-1,4-benzoxazin-3(4*H*)-one is represented by the following structure:



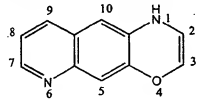
A 2*H*-1,4-benzoxazine is represented by the following structure:



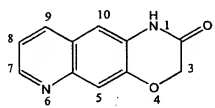
A 7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one is represented by the following structure:



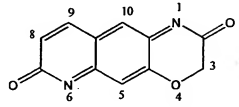
A 1*H*-[1,4]oxazino[3,2-*g*]quinoline is represented by the following structure:



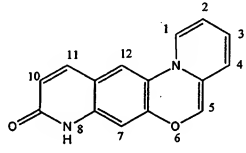
A 1*H*-[1,4]oxazino[3,2-*g*]quinoline-2(3*H*)-one is represented by the following structure:



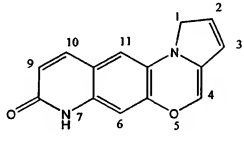
A **3*H*-[1,4]oxazino[3,2-*g*]quinolin-2,7-dione** is represented by the following structure:



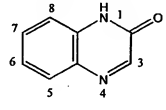
A **pyrido[1',2':4,5][1,4]oxazino[3,2-*g*]quinolin-9(8*H*)-one** is represented by the following structure:



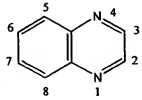
A **1*H*-pyrrolo[1',2':4,5][1,4]oxazino[3,2-g]quinolin-8(7*H*)-one** is represented by the following structure:



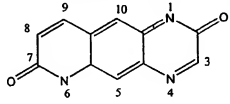
A **quinoxalin-2(1*H*)-one** is represented by the following structure:



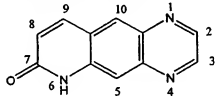
A **quinoxaline** is represented by the following structure:



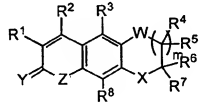
A **pyrazino[3,2-*g*]quinolin-2,7-dione** is represented by the following structure:



A **pyrazino[3,2-*g*]quinolin-7(6*H*)-one** is represented by the following structure:

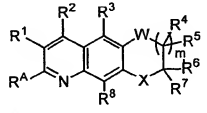


Compounds of the present invention are represented by those having the formulas:



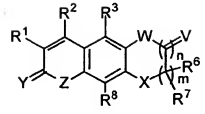
(I)

OR



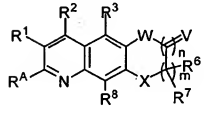
(II)

OR



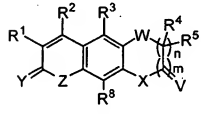
(III)

OR



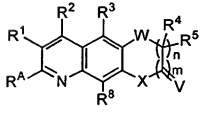
(IV)

OR



(V)

OR



(VI)

wherein:

R^1 represents hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_mR^9$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl, wherein the alkyl, cycloalkyl,

heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups may be optionally substituted;

R^2 is hydrogen, F, Cl, Br, I, CF_3, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl, wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups may be optionally substituted;

R^3 is hydrogen, F, Cl, Br, I, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, or $C_1 - C_6$ alkyl, $C_1 - C_6$ heteroalkyl, or $C_1 - C_6$ haloalkyl and wherein the alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted;

R^4 and R^5 each independently are hydrogen, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl, wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups may be optionally substituted; or

R^4 and R^5 taken together can form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted;

R^6 and R^7 each independently are hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl, wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups may be optionally substituted; or

R^6 and R^7 taken together can form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted; or

R^6 and R^5 taken together can form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted;

R^8 is hydrogen, C_1 - C_4 alkyl, C_1 – C_4 heteroalkyl, C_1 – C_4 haloalkyl, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$ or $S(O)_mR^9$, wherein the alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted;

R^9 is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_2 – C_8 alkenyl or arylalkyl, wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups may be optionally substituted;

R^{10} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_2 – C_8 alkenyl, arylalkyl, SO_2R^{12} or $S(O)R^{12}$, wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups may be optionally substituted;

R^{11} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_2 – C_8 alkenyl or arylalkyl, wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups may be optionally substituted;

R^{12} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_2 – C_8 alkenyl or arylalkyl, wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups may be optionally substituted;

R^{13} is hydrogen, C_1 – C_8 alkyl, C_3 – C_8 cycloalkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, aryl, heteroaryl, or arylalkyl, wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl and arylalkyl groups may be optionally substituted; or

R^{13} and R^4 taken together can form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted;

R^{14} and R^{15} each independently are hydrogen, C_1 – C_8 alkyl, C_3 – C_8 cycloalkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, aryl, heteroaryl, arylalkyl, C_2 – C_8 alkynyl or C_2 – C_8 alkenyl, wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, alkynyl and alkenyl groups may be optionally substituted;

R^A is F, Br, Cl, I, CN, $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{17}R^{17}$, SOR^{17} or SO_2R^{17}, wherein the alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted;

R^{16} is hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, COR^{17}, CO_2R^{17} or $CONR^{17}R^{17}$, wherein the alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted;

R^{17} is hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl or C_1-C_4 heteroalkyl, wherein the alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted;

m is 0, 1 or 2;

n is 1 or 2;

V is O, S or $CR^{14}R^{15}$;

W is O, $S(O)_m$, NR^{13}, $NC(Y)R^{11}$, or NSO_2R^{11}

X and Z each independently are O, $S(O)_m$, NR^{11}, $NC(Y)R^{11}$, NSO_2R^{12} or $NS(O)R^{12}$;

Y is O or S; and

any two of R^4, R^5, R^6, R^7, and R^{13} taken together can form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted;

and pharmaceutically acceptable salts thereof.

Preferred R^1 groups include hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_mR^9$, $C_1 - C_8$ alkyl, $C_1 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, allyl, $C_1 - C_8$ aryl, $C_1 - C_8$ arylalkyl, $C_1 - C_8$ heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl. The alkyl, cycloalkyl, heteroalkyl, haloalkyl, allyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^1 groups include H, F, Cl, OR^9, $NR^{10}R^{11}$, $S(O)_mR^9$, and C_1-C_2 alkyl. Particularly preferred R^1 groups include H, F, and Cl.

Preferred R^2 groups include hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$,

heteroalkyl, $C_1 - C_8$ haloalkyl, allyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl. The alkyl, cycloalkyl, heteroalkyl, haloalkyl, allyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^2 groups include H, F, Cl, methyl, ethyl, CF_3, CF_2H, CF_2Cl, CFH_2, and OR^9. Particularly preferred R^2 groups include H, Cl, methyl, ethyl, CF_3, CF_2H, CF_2Cl.

Preferred R^3 groups include hydrogen, F, Cl, Br, I, OR^9, $S(O)mR^9$, $NR^{10}R^{11}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl and C_1-C_6 haloalkyl. The alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted. More preferred R^3 groups include hydrogen, F, Cl, OR^9, $NR^{10}R^{11}$, and $S(O)_mR^9$.

Preferred R^4 groups include H, OR^9, $C(Y)OR^{11}$, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, arylalkyl, and heteroaryl. The alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkynyl, alkenyl, aryl, arylalkyl and heteroaryl groups may be optionally substituted. More preferred R^4 groups include H, OR^9, $C(Y)OR^{11}$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_4 haloalkyl, C_2-C_4 alkynyl, and C_2-C_4 alkenyl. Particularly preferred R^4 groups include H, OR^9, $C(Y)OR^{11}$, C_1-C_4 alkyl, C_1-C_4 haloalkyl, and where R^4 and R^{13} together form a five- or six- membered ring.

Also preferred are compounds where R^4 and R^{13} together form a saturated or unsaturated three- to seven-membered ring optionally substituted with 1-2 substituents. Examples of such substituents include, for example, hydrogen, F, Cl, Br, C_1-C_4 alkyl, C_3-C_8 cycloalkyl, C_1-C_4 heteroalkyl, C_1-C_4 haloalkyl, OR^9 and $NR^{10}R^{11}$. The alkyl, cycloalkyl, heteroalkyl, haloalkyl groups may be optionally substituted.

Also preferred are compounds where R^4 and R^{13} together form a five- to seven-membered ring optionally substituted with 1-2 substituents. Examples of such substituents include F, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_4 haloalkyl, and OR^9. The alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted.

Preferred R^5 groups include H, OR^9, $C(Y)OR^{11}$, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, arylalkyl, and heteroaryl. The alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkynyl, alkenyl, aryl, arylalkyl and heteroaryl groups may be optionally substituted. More preferred R^5 groups include hydrogen, OR^9, $C(Y)OR^{11}$, C_1-C_4 alkyl, and C_1-C_4 haloalkyl.

Also preferred are compounds where R^4 and R^5 taken together form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted.

Preferred R^6 groups include hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, allyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, arylalkyl and heteroaryl. The alkyl, cycloalkyl, allyl, heteroalkyl, haloalkyl, alkynyl, alkenyl, aryl, arylalkyl and heteroaryl groups may be optionally substituted. More preferred R^6 groups include hydrogen, CH_3, and CH_2CH_3.

Also preferred are compounds where R^6 and R^5 taken together form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted.

Preferred R^7 groups include hydrogen, C_1-C_8 alkyl, C_3-C_8 cycloalkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, arylalkyl and heteroaryl. The alkyl, cycloalkyl, heteroalkyl, haloalkyl, alkynyl, alkenyl, aryl, arylalkyl and heteroaryl groups may be optionally substituted. More preferred R^7 groups include hydrogen, CH_3, and CH_2CH_3.

Also preferred are compounds where R^6 and R^7 taken together form a saturated or unsaturated three- to seven-membered ring that may be optionally substituted.

Preferred R^8 groups include hydrogen, F, Cl, Br, I, NO_2, OR^9, $S(O)_mR^9$, C_1-C_4 alkyl, C_1-C_4 heteroalkyl, C_1-C_4 haloalkyl, and $NR^{10}R^{11}$. The alkyl, heteroalkyl and haloalkyl groups may be optionally substituted. More preferred R^8 groups include hydrogen and F.

Preferred R^9 groups include hydrogen, $C(Y)R^{12}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, arylalkyl, C_2-C_8 alkynyl and C_2-C_8 alkenyl. The alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^9 groups include hydrogen, $C(Y)R^{12}$, and C_1-C_6 alkyl. Particularly preferred R^9 groups include CH_3, CH_2CH_3, $CH_2CH_2CH_3$, and $C(O)CH_3$.

Preferred R^{10} groups include hydrogen, $C(Y)R^{12}$, $C(Y)OR^{12}$, SO_2R^{12}, $S(O)R^{12}$, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, arylalkyl, C_2-C_8 alkynyl, and C_2-C_8 alkenyl. The alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^{10} groups include hydrogen, C_1-C_6 alkyl, $C(Y)R^{12}$, $C(Y)OR^{12}$, SO_2R^{12}.

Preferred R^{11} groups include hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, arylalkyl, C_2-C_8 alkynyl, and C_2-C_8 alkenyl. The alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^{11} groups include hydrogen and C_1-C_4 alkyl.

Preferred R^{12} groups include hydrogen, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, aryl, heteroaryl, allyl, arylalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl. The alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, allyl, arylalkyl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^{12} groups include hydrogen and C_1-C_4 alkyl.

Preferred R^{13} groups include hydrogen, C_1-C_8 alkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_3-C_8 cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, C_2-C_8 alkynyl, and C_2-C_8 alkenyl. The alkyl, heteroalkyl, haloalkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^{13} groups include C_1-C_4 alkyl, C_2-C_4 alkenyl, C_2-C_4 alkynyl, C_1-C_4 heteroalkyl and C_1-C_4 haloalkyl. Particularly preferred R^{13} groups include CH_3, CH_2CH_3, $CH_2CH_2CH_3$, $CH(CH_3)_2$, $CH_2CH_2(CH_3)$, CH_2(cyclopropyl), CH_2CClF_2, CH_2CHF_2, and CH_2CF_3.

Preferred R^{14} groups include hydrogen, C_1-C_8 alkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, arylalkyl, and heteroaryl. The alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^{14} groups include hydrogen and C_1-C_4 alkyl.

Preferred R^{15} groups include hydrogen, C_1-C_8 alkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, arylalkyl, and heteroaryl. The alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^{15} groups include hydrogen and C_1-C_4 alkyl.

Preferred R^{16} groups include hydrogen, C_1-C_8 alkyl, C_1-C_8 heteroalkyl, C_1-C_8 haloalkyl, C_2-C_8 alkynyl, C_2-C_8 alkenyl, COR^{17}, CO_2R^{17}, $CONR^{17}R^{17}$, aryl, and heteroaryl. The alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkynyl, and alkenyl groups may be optionally substituted. More preferred R^{16} groups include hydrogen and C_1-C_4 alkyl.

Preferred R^A groups include hydrogen, F, Cl, Br, I, CN, C_1-C_6 alkyl, C_1-C_6 heteroalkyl, C_1-C_6 haloalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17},

$CONR^{17}R^{17}$, SOR^{17}, and SO_2R^{17}. The alkyl, heteroalkyl, and haloalkyl groups may be optionally substituted. More preferred R^A groups include hydrogen, F, Cl, CN, and OR^{16}.

Preferably n is 1 or 2. More preferably, n is 1.

Preferably, m is 1 or 2. More preferably, m is 1.

Preferred V groups include O and S. More preferably, V is O.

Preferred W groups include O, $S(O)_m$, NR^{13}, $NC(Y)R^{11}$, and NSO_2R^{11}. More preferred W groups include NR^{13}, $NC(Y)R^{11}$, and NSO_2R^{11}. Particularly preferred W groups include NR^{13}.

Preferred X groups include O, $S(O)_m$, NR^{11}, $NC(Y)R^{11}$, NSO_2R^{12} and $NS(O)R^{12}$. More preferred X groups include O, $S(O)_m$, and NR^{11}. Particularly preferred X groups include O and $S(O)_m$. Most preferably, X is O.

Preferably Y is O.

Preferred Z groups include O, $S(O)_m$, NR^{11}, $NC(Y)R^{11}$, NSO_2R^{12} and $NS(O)R^{12}$. More preferred Z groups include O, $S(O)_m$, and NR^{11}. Most preferably, Z is NH.

In one aspect, compounds of formula I are preferred.

In another aspect, compounds of formula II are preferred.

In still another aspect, compounds of formula III are preferred.

In yet another aspect, compounds of formula IV are preferred.

In one preferred aspect, R^3 and R^8 are each hydrogen; X and Y are each independently O or S; W is NR^{13}; and Z is NR^{11}.

In another preferred aspect, R^3 and R^8 are each hydrogen; X and Y are each O, W is NR^{13}; and Z is NR^{11}.

In still another preferred aspect, R^3 and R^8 are each hydrogen; R^2 is CF_3, X and Y are each O, W is NR^{13}; and Z is NR^{11}.

In yet another preferred aspect, R^1 R^3, R^4, R^5, R^6, R^7, R^8, R^{11} and R^A are each hydrogen, R^2 is CF_3, R^{13} is C_1-C_8 alkyl, W is NR^{13}, Z is NR^{11}, X and Y are each O; and m is 1 or 2.

In yet another preferred aspect, R^1 R^3, R^6, R^7, R^8, R^{11} and R^A are each hydrogen, R^2 is CF_3, R^4 ,R^5 and R^{13} are each C_1-C_8 alkyl, W is NR^{13}, Z is NR^{11}, X and Y are each O; and m is 1 or 2.

In yet another preferred aspect, R^1 R^3, R^4, R^5, R^8, R^{11} and R^A are each hydrogen, R^2 is CF_3, R^6 ,R^7 and R^{13} are each C_1-C_8 alkyl, W is NR^{13}, Z is NR^{11}, X and Y are each O; and m is 1 or 2.

In a preferred aspect, the present invention provides a pharmaceutical compositions comprising an effective amount of an androgen receptor modulating compound of formulas I through VI shown above wherein R^1 through R^{17}, R^A, V, W, X, Y, Z, m and n all have the same definitions as given above.

In a further preferred aspect, the present invention comprises methods of modulating processes mediated by androgen receptors comprising administering to a patient an effective amount of a compound of the formulas I through VI shown above, wherein R^1 through R^{17}, R^A, V, W, X, Y, Z, m and n all have the same definitions as those given above.

Any of the compounds of the present invention can be synthesized as pharmaceutically acceptable salts for incorporation into various pharmaceutical compositions. As used herein, pharmaceutically acceptable salts include, for example, hydrochloric, hydrobromic, hydroiodic, hydrofluoric, sulfuric, citric, maleic, acetic, lactic, nicotinic, succinic, oxalic, phosphoric, malonic, salicylic, phenylacetic, stearic, pyridine, ammonium, piperazine, diethylamine, nicotinamide, formic, urea, sodium, potassium, calcium, magnesium, zinc, lithium, cinnamic, methylamino, methanesulfonic, picric, tartaric, triethylamino, dimethylamino, and tris(hydroxymethyl)aminomethane. Additional pharmaceutically acceptable salts are known to those skilled in the art.

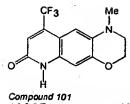
AR agonist, partial agonist and antagonist compounds (including compounds with tissue-selective AR modulator activity) of the present invention will prove useful in the treatment of acne (antagonist), male-pattern baldness (antagonist), male hormone replacement therapy (agonist), wasting diseases (agonist), hirsutism (antagonist), stimulation of hematopoiesis (agonist), hypogonadism (agonist), prostatic hyperplasia (antagonist), osteoporosis (agonist) male contraception (agonist), impotence (agonist), sexual dysfunction (agonist), cancer cachexia (agonist), various hormone-dependent cancers, including, without limitation, prostate (antagonist) and breast cancer and as anabolic agents (agonist). It is understood by those of skill in the art that a partial agonist

may be used where agonist activity is desired, or where antagonist activity is desired, depending upon the AR modulator profile of the particular partial agonist.

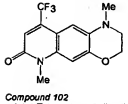
It is understood by those skilled in the art that while the compounds of the present invention will typically be employed as a selective agonists, partial agonists or antagonists, that there may be instances where a compound with a mixed steroid receptor profile is preferred. For example, use of a PR agonist (i.e., progestin) in female contraception often leads to the undesired effects of increased water retention and acne flare-ups. In this instance, a compound that is primarily a PR agonist, but also displays some AR and MR modulating activity, may prove useful. Specifically, the mixed MR effects would be useful to control water balance in the body, while the AR effects would help to control any acne flare-ups that occur.

Furthermore, is understood by those skilled in the art that the compounds of the present invention, including pharmaceutical compositions and formulations containing these compounds, can be used in a wide variety of combination therapies to treat the conditions and diseases described above. Thus, the compounds of the present invention can be used in combination with other hormones and other therapies, including, without limitation, chemotherapeutic agents such as cytostatic and cytotoxic agents, immunological modifiers such as interferons, interleukins, growth hormones and other cytokines, hormone therapies, surgery and radiation therapy.

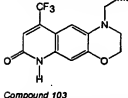
Representative AR modulator compounds (i.e., agonists and antagonists) according to the present invention include:



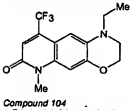
Compound 101
1,2,3,6-Tetrahydro-1-methyl-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



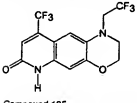
Compound 102
1,2,3,6-Tetrahydro-1,6-dimethyl-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



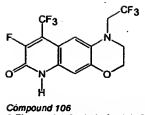
Compound 103
1-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



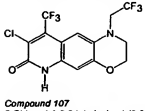
Compound 104
1-Ethyl-1,2,3,6-tetrahydro-6-methyl-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



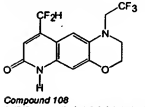
Compound 105
1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



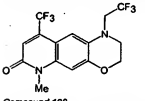
Compound 106
8-Fluoro-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



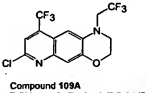
Compound 107
8-Chloro-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



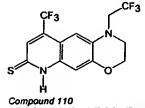
Compound 108
9-(Difluoromethyl)-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



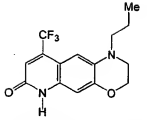
Compound 109
1,2,3,6-Tetrahydro-6-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



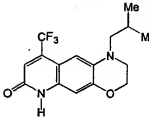
Compound **109A**
7-Chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1H-[1,4]oxazino[3,2-g]quinoline



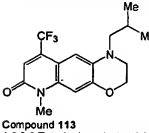
Compound 110
1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)7H-[1,4]oxazino[3,2-g]quinolin-7-thione



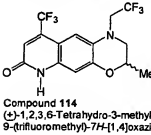
Compound **111**
1,2,3,6-Tetrahydro-1-propyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



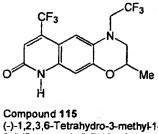
Compound **112**
1,2,3,6-Tetrahydro-1-isobutyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



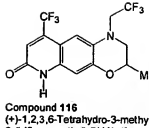
Compound **113**
1,2,3,6-Tetrahydro-1-isobutyl-6-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



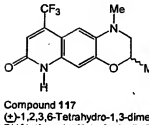
Compound **114**
(+)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



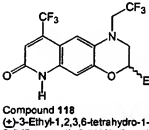
Compound **115**
(-)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



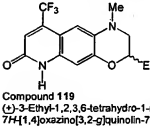
Compound **116**
(+)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



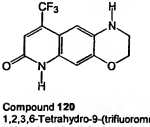
Compound **117**
1,2,3,6-Tetrahydro-1,3-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



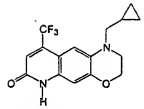
Compound **118**
(+)-3-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



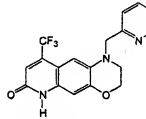
Compound **119**
(+)-3-Ethyl-1,2,3,6-tetrahydro-1-methyl-9-(trifluoromethyl)7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



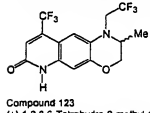
Compound **120**
1,2,3,6-Tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



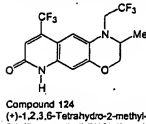
Compound 121
1-Cyclopropylmethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



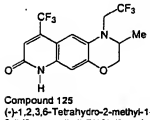
Compound 122
1,2,3,6-Tetrahydro-1-(pyridylmethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



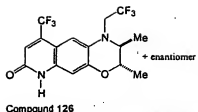
Compound 123
(±)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



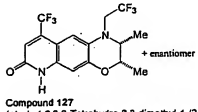
Compound 124
(+)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



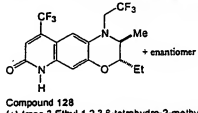
Compound 125
(-)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



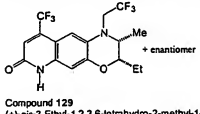
Compound 126
(±)-*trans*-1,2,3,6-Tetrahydro-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



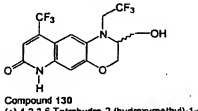
Compound 127
(±)-*cis*-1,2,3,6-Tetrahydro-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



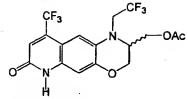
Compound 128
(±)-*trans*-3-Ethyl-1,2,3,6-tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



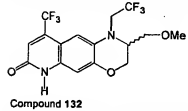
Compound 129
(±)-*cis*-3-Ethyl-1,2,3,6-tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



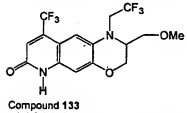
Compound 130
(±)-1,2,3,6-Tetrahydro-2-(hydroxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



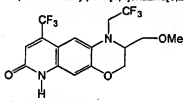
Compound **131**
(+)-1,2,3,6-Tetrahydro-2-(acetoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



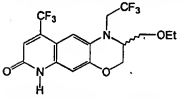
Compound **132**
(+)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



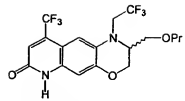
Compound **133**
(+)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



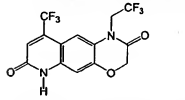
Compound **134**
(-)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



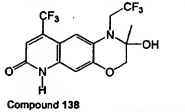
Compound **135**
(+)-2-(Ethoxymethyl)-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



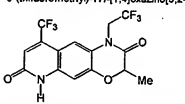
Compound **136**
(+)-1,2,3,6-Tetrahydro-2-(propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



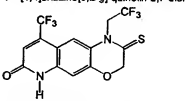
Compound **137**
1,2-Dihydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-3*H*-[1,4]oxazino[3,2-*g*]quinolin-2,7-dione



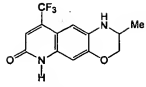
Compound **138**
(+)-1,2,3,6-Tetrahydro-2-hydroxy-2-methyl-1-(2,2,2-trifluoroethyl 9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



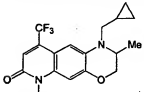
Compound **139**
1,2-Dihydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-3*H*-[1,4]oxazino[3,2-*g*]-quinolin-2,7-dione



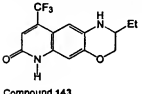
Compound **140**
1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-2-thioxo-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



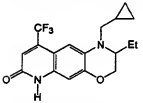
Compound **141**
(+)-1,2,3,6-Tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



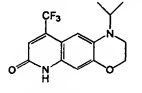
Compound **142**
1-Cyclopropylmethyl-1,2,3,6-tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



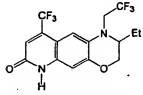
Compound **143**
(+)-2-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



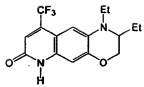
Compound **144**
1-Cyclopropylmethyl-2-ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



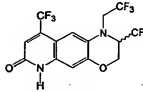
Compound **144A**
1,2,3,6-Tetrahydro-1-isopropyl-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-g]quinolin-7-one



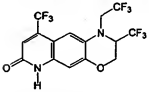
Compound **145**
(+)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



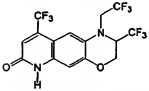
Compound **146**
(±)-1,2-Diethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



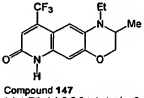
Compound **146A**
(+)-1,2,3,6-Tetrahydro-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



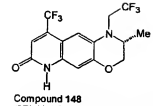
Compound **146B**
(+)-1,2,3,6-Tetrahydro-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



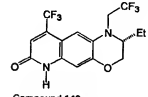
Compound **146C**
(-)-1,2,3,6-Tetrahydro-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



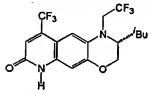
Compound **147**
(+)-1-Ethyl-1,2,3,6-tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



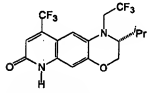
Compound **148**
(2R)-(-)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



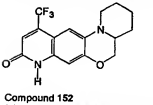
Compound **149**
(2R)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



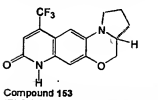
Compound **150**
(2R)-1,2,3,6-Tetrahydro-2-isobutyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



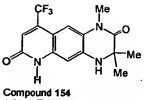
Compound **151**
(2R)-1,2,3,6-Tetrahydro-2-isopropyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one



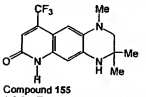
Compound **152**
(+)-1,2,3,4,4a,5-Hexahydro-11-(trifluoromethyl)-pyrido[1',2':4,5][1,4]oxazino[3,2-*g*]quinolin-9(8*H*)-one



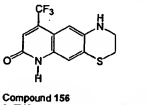
Compound **153**
(R)-2,3,3a,4-Tetrahydro-10-(trifluoromethyl)-pyrrolo[1',2':4,5][1,4]oxazino[3,2-*g*]quinolin-8(7*H*)-one



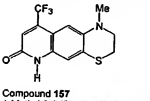
Compound **154**
1,3,4,6-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)-pyrazino[3,2-*g*]quinolin-2,7-dione



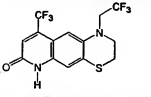
Compound **155**
1,2,3,4-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)-pyrazino[3,2-*g*]quinolin-7(6*H*)one



Compound **156**
9-(Trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one

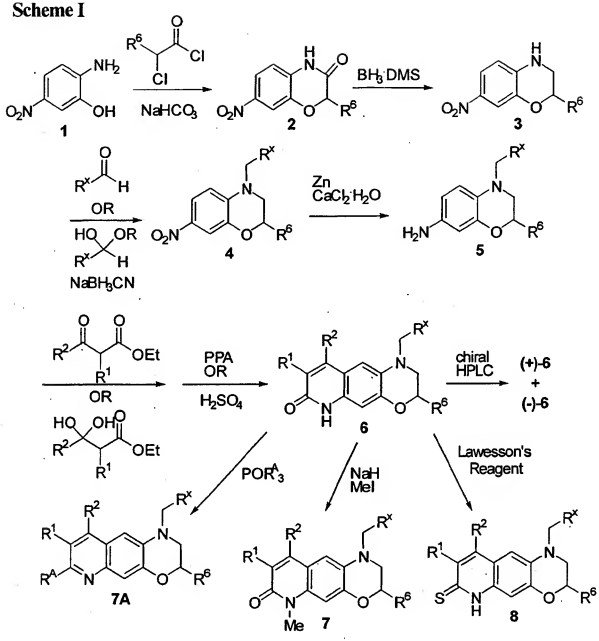


Compound **157**
1-Methyl-9-(trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one



Compound **158**
1-(2,2,2-Trifluoroethyl)-9-(trifluoromethyl)-1,2,3,6-tetrahydr 7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one

Scheme I



Compounds of the present invention, comprising classes of heterocyclic nitrogen compounds and their derivatives, can be obtained by routine chemical synthesis by those skilled in the art, e.g., by modification of the heterocyclic nitrogen compounds disclosed or by a total synthesis approach.

The sequences of steps for several general schemes to synthesize the compounds of the present invention are shown below. In each of the schemes the R groups (e.g., R^1,

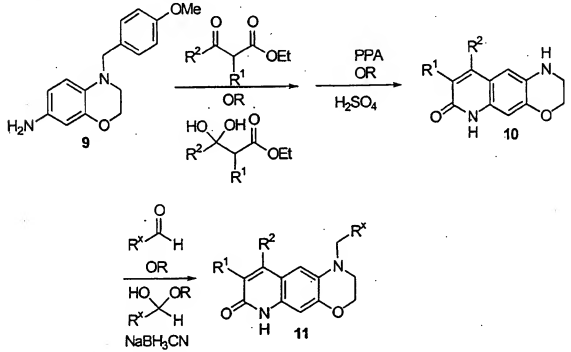
R^2, etc.) correspond to the specific substitution patterns noted in the Examples. However, it will be understood by those skilled in the art that other functionalities disclosed herein at the indicated positions of compounds of formulas I through VI also comprise potential substituents for the analogous positions on the structures within the schemes.

The synthesis of 7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one compounds (e.g., Structures **6** and **7**), is depicted in **Scheme I**. The process of **Scheme I** begins with a cyclization of a haloacetyl halide onto 2-amino-5-nitrophenol (Structure **1**) with, for example, chloroacetyl chloride to afford a lactam (Structure 2). See D. R. Shridhar, *et al.*, *Org. Prep. Proc. Int.*, 14:195 (1982). The amide is then reduced to the corresponding amine (Structure **3**), with, for example, borane dimethyl sulfide. See Y. Matsumoto , *et. al.*, *Chem. Pharm. Bull.*, 44:103-114 (1996). Treatment of a compound such as Structure **3** with an aldehyde or its corresponding hydrate or hemiacetal, for example trifluoroacetaldehyde hydrate in the presence of a reducing agent, for example, sodium cyanoborohydride, in a carboxylic acid, for example trifluoroacetic acid, affords a compound such as Structure **4**. The nitro derivative is reduced to the corresponding aniline, with a reducing agent, for example, zinc and calcium chloride, to afford Structure **5**. Treatment of the aniline with a β-ketoester or corresponding hydrate, for example 4,4,4-trifluoroacetoacetate, at elevated temperatures, followed by treatment with an acid, for example, sulfuric acid, affords a major product (Structure **6**). The cyclization of anilines as described above is known as a Knorr cyclization. See, G. Jones, *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W., eds. Pergamon, New York, 1984. Vol. 2, chap. 2.08, pp 421-426, the disclosure of which is herein incorporated by reference. In turn, the quinolinone nitrogen may be alkylated by, for example, treatment with sodium hydride followed by iodomethane, to afford a compound of Structure **7**. Alternatively, a quinolinone compound of Structure **6** can be converted to the corresponding quinoline by treatment with a dehydrating agent, for example, oxyphosphoryl chloride, to afford a compound of Structure **7A**.

Alternatively, a quinolinone compound of Structure **6** can be transformed to the corresponding thio-compound by treatment with, for example, Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide] to give a 7*H*-

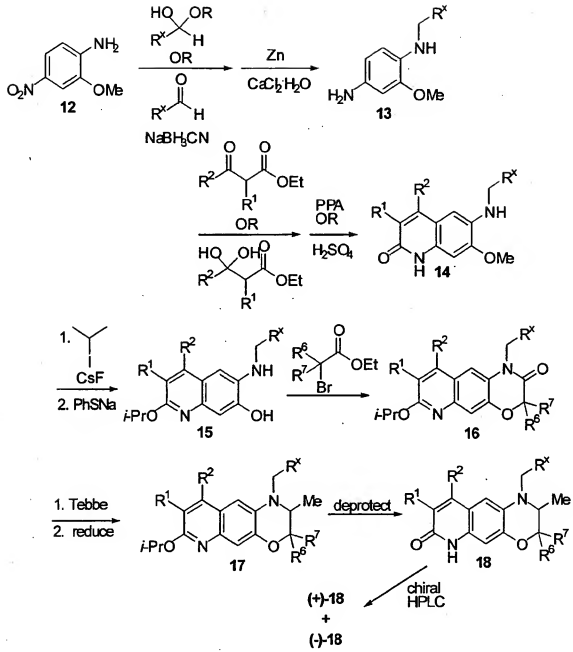
[1,4]oxazino[3,2-*g*]quinolin-thione (e.g., Structure **8**). See J. Voss, *Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed. John Wiley and Sons, New York, 1995; Vol. 1, pp 530-533, the disclosure of which is herein incorporated by reference. Alternatively, a compound of Structure **6** (or chiral synthetic precursors of Structure **6**) can be separated into its corresponding enantiomers, (+)-**6** and (-)-**6** by chiral HPLC, with, for example, a preparative Chiralpak AD column eluted with hexanes:isopropanol.

Scheme II



An alternate synthesis of 7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one compounds (e.g., Structures **10** and **11**) is shown in **Scheme II**. The process of **Scheme II** begins with a Knorr cyclization of 7-amino-3,4-dihydro-4-*p*-methoxybenzyl-2H-1,4-benzoxazine, and a β-ketoester promoted by an acid, for example, sulfuric acid to afford a compound of Structure **10**. Alkylation of the quinolinone nitrogen may be achieved by treatment with an aldehyde or its corresponding hydrate, for example cyclopropanecarboxaldehyde in the presence of a reducing agent, for example, sodium cyanoborohydride, to afford the alkylated derivative of the corresponding quinolinone compound (e.g., Structure **11**).

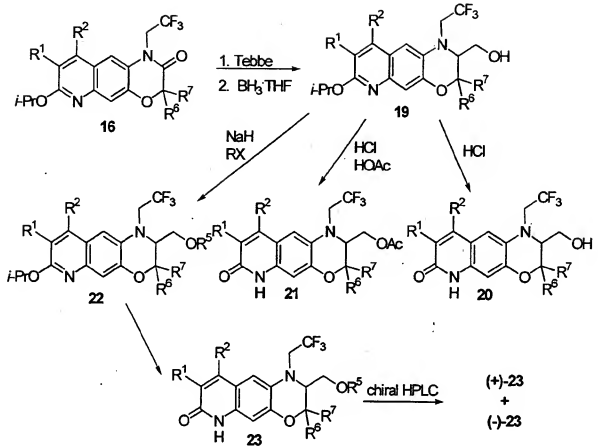
Scheme III



An additional synthetic route into quinoline compounds (e.g., Structures **16** and **18**) is shown in **Scheme III**. The process of **Scheme III** begins with reductive amination of 2-methoxy-4-nitroaniline with an aldehyde or its corresponding hydrate, for example trifluoroacetaldehyde hydrate in the presence of a reducing agent, for example, sodium cyanoborohydride, in an acid, for example trifluoroacetic acid, to afford the

corresponding *N*-alkylated amine. The nitro derivative is reduced to the corresponding aniline, with a reducing agent, for example, zinc and calcium chloride, to afford a compound of Structure **13**. Knorr cyclization of the aniline by heating with a β-ketoester or corresponding hydrate, for example 4,4,4-trifluoroacetoacetate, followed by treatment with an acid, for example, sulfuric acid, affords a product of Structure **14**. Protection of the pyridone ring, with, for example isopropyl iodide mediated by a base, for example, cesium fluoride, affords the corresponding imino ether. See T. Sato, *et al.*, *Synlett* **1995**, 845-846. Demethylation of the anisole is accomplished by treatment with, for example, sodium thiophenolate to afford a compound of Structure **15**. See C. Hansson, *et al.*, *Synthesis* **1975**, 191. Treatment of aminophenol derivative **15** with an α-bromoester, for example, ethyl bromoacetate, and a base, with for example, potassium carbonate, affords a quinolinone compound (Structure **16**). Treatment of quinolinone compounds such as Structure **16** with an alkylidenation reagent, for example, Tebbe's reagent, followed by reduction with, for example, sodium cyanoborohydride, in an acid, for example acetic acid, affords a quinoline compound (e.g., Structure **17**). See S. H. Pine, *et. al.*, *J. Org. Chem.* **1985**, *50*, 1212, for the methylenation of amides. Deprotection can be accomplished in one of two ways. Treatment of the iminoether (Structure **17**) with a mineral acid, for example hydrochloric acid, affords a 7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one compound (Structure **18**). Alternatively, this transformation can be carried out with a Lewis acid, for example boron trichloride, to afford Structure **18**. See T. Sala, *et al.*, *J. Chem. Soc., Perkin Trans. I*, **1979**, 2593. Quinolinone compounds of Structure **18** (or any chiral synthetic precursor of **18**) can be separated into their corresponding enantiomers, (+)-**18** and (-)-**18** by chiral HPLC, with, for example, a preparative Chiralpak AD column eluted with hexanes:isopropanol.

Scheme IV

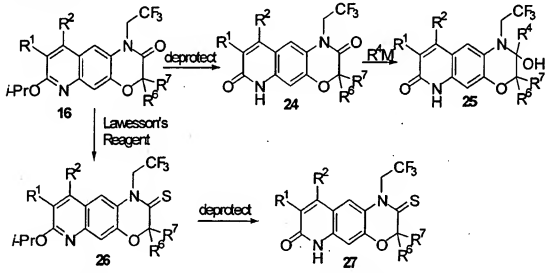


The process of converting quinolinone compounds (e.g., Structure **16**) into corresponding hydroxyalkyl quinoline compounds (e.g., Structure **19**) and then further converting into corresponding hydroxyalkyl, acyloxyalkyl, and alkyloxyalkyl quinolinone derivatives (e.g., Structures **20**, **21**, and **23** respectively) is shown in **Scheme IV**. The process of **Scheme IV** begins with a Tebbe olefination of a quinolinone compound (e.g., Structure **16**) followed by hydroboration of the resultant enamine to afford a hydroxyalkyl quinoline compound (Structure **19**). See C. T. Goralski, *et. al. Tetrahedron Lett.* **1994**, *35*, 3251, for the hydroboration of enamines. Hydrolysis of the imino ether with an acid, for example hydrochloric acid, affords a hydroxy quinolinone compound (e.g., Structure **20**).

Alternatively, hydrolysis of the imino ether of a hydroxyalkyl quinoline compound (e.g., Structure **19**) can be carried out with an acid, for example hydrochloric acid, in acetic acid, to afford an acyloxyalkyl quinolinone compound (Structure **21**)

Alternatively, a hydroxy quinoline compound (e.g., Structure **19**) can be *O*-alkylated by treatment with a base, for example, sodium hydride, and an alkylating agent, with, for example methyl iodide, to afford an alkoxyalkyl quinoline compound (e.g., Structure **22**). Imino ether hydrolysis of Structure **22** with an acid, for example hydrochloric acid in acetic acid, affords an alkoxyalkyl quinoline compound (Structure **23**). Compound such as Structures **20**, **21**, or **23** can be separated into their corresponding enantiomers, (+)-**20** and (-)-**20**, (+)-**21** and (-)-**21**, or (+)-**23** and (-)-**23** by chiral HPLC, with, for example, a preparative Chiralpak AD column eluted with hexanes:isopropanol.

Scheme V

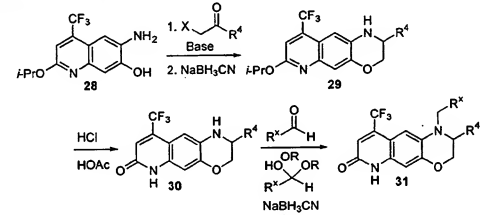


Quinolinone compounds (e.g., Structure **16**) may be converted into corresponding quinoline-diones (e.g., Structure **24**), hydroxy quinolinones (e.g., Structure **25**), and quinoline-thiones (e.g., Structures **26** and **27**) by the processes shown in **Scheme V**. The process of **Scheme V** begins with the deprotection of the imino ether of Structure **16** by treatment with a mineral acid, for example, hydrochloric acid, to afford a quinoline-dione compound of Structure **24**. Alternatively, this transformation can be carried out with a Lewis acid, for example, boron trichloride, to afford a quinoline-dione compound (e.g., Structure **24**). See T. Sala, et al., *supra*. A quinoline-dione compound (e.g., Structure

24) can be converted to a hydroxy quinoline compound (e.g., Structure 25) by addition of an organometallic reagent, for example, methyl lithium, which affords a hydroxy quinoline compound (Structure 25).

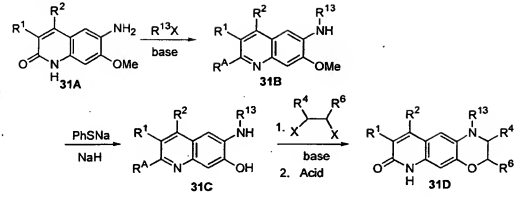
Quinoline compounds (e.g., Structure 16) can optionally be converted into corresponding thio-compounds (e.g., Structure 25) by treatment with, for example, Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide]. Hydrolysis of the imino ether with a Lewis acid, for example, boron trichloride, affords a quinoline-thione compound (Structure 26).

Scheme VI



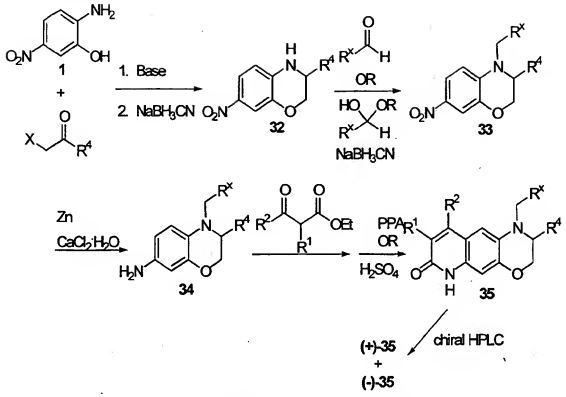
A synthesis of quinolinone compounds such as Structure 30 is shown in **Scheme VI**. The process of **Scheme VI** begins with the O-alkylation of an o-aminophenol, for example, a 6-amino-7-hydroxyquinoline, with a haloketone, for example, chloroacetone, mediated by a base, for example, potassium carbonate, followed by treatment with a reducing agent, for example, sodium cyanoborohydride, in an acid, for example, acetic acid, to afford a quinoline compound of Structure 29. Hydrolysis of the imino ether of Structure 29 with an acid, for example, hydrochloric acid in acetic acid, affords a quinolinone compound of Structure 30. Alkylation of the quinolinone nitrogen is achieved by treatment of quinolinone compounds (e.g., Structure 30) with an aldehyde or its corresponding hydrate, for example, cyclopropanecarboxaldehyde, with a reducing agent, for example, sodium cyanoborohydride, in an acid, for example, acetic acid, affords a compound of Structure 31.

Scheme VIA



An additional route to quinolinone compounds such as Structure **31D** is shown in **Scheme VIA**. The process of **Scheme VIA** begins with the alkylation of a 6-aminoquinolinone with, for example, 6-amino-7-methoxy-4-trifluoromethyl-1*H*-quinolin-2-one, with an alkyl halide, for example, isopropyl iodide, mediated by a base, for example, cesium fluoride, to afford a compound of structure **31B**. Demethylation of the methyl ether is accomplished by treatment with, for example, sodium thiophenolate to afford a compound of Structure **31C**. Annulation of the oxazine ring can be accomplished by treatment with a vicinal dihalide, for example, 1,2-dibromoethane, mediated by a base, for example potassium carbonate, to afford the corresponding 1,4-oxazine, which in turn is converted to a compound of Structure **31D** by treatment with an acid, for example, hydrochloric acid in acetic acid at elevated temperatures.

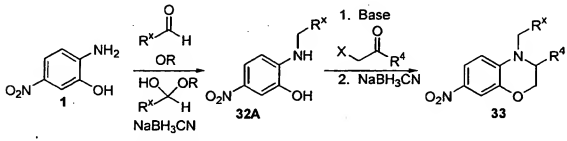
Scheme VII



Quinolinones (e.g., Structure **35**) are prepared from benzoxazines (e.g., Structure **34**) by the synthetic route outlined in **Scheme VII**. **Scheme VII** begins with an alkylation of a haloketone onto 2-amino-5-nitrophenol (Structure **1**) with, for example, 2-bromobutanone, mediated by a base, for example, potassium carbonate, followed by treatment with a reducing agent, for example, sodium cyanoborohydride, in an acid, for example acetic acid, to afford a benzoxazine compound (e.g., Structure **32**). The benzoxazine is alkylated at the benzoxazine nitrogen by treatment of a benzoxazine compound (e.g., Structure **32**) with an aldehyde, its corresponding hydrate or hemiacetal, with for example, trifluoroacetaldehyde hydrate in the presence of a reducing agent, for example, sodium cyanoborohydride, in an acid, for example trifluoroacetic acid. This procedure affords an alkylated benzoxazine compound (e.g., Structure **33**). The nitro derivative of the alkylated benzoxazine compound (Structure **33**) is reduced to the corresponding aniline by catalytic hydrogenation or with a reducing agent, for example, zinc and calcium chloride, to afford benzoxazine compound (e.g., Structure **34**). Knorr cyclization of an aminobenzoxazine (e.g., Structure **34**) by heating with a β-ketoester or

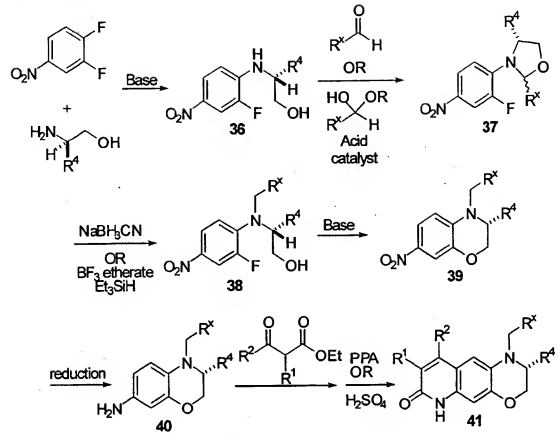
corresponding hydrate, with for example, 4,4,4-trifluoroacetoacetate, followed by treatment with an acid, for example, sulfuric acid, affords a quinolinone product (e.g., Structure **35**).

Scheme VIIA



Compounds such as the 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazines of Structure **33** are key intermediates in the preparation of quinolinones and other fused ring structures. In accordance with the current invention, we have developed a method to prepare these 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazines in enantiomerically pure form (Structure **39**) from optically pure β-aminoalcohols. A synthetic method for the preparation of enantiomerically pure, fused ring compounds, such as quinolinones **41**, that relies upon such intermediates is shown in **Scheme VIII**.

Scheme VIII

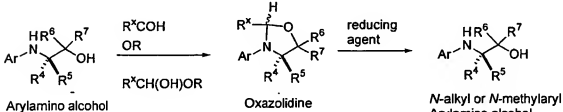


The asymmetric synthesis of **Scheme VIII** begins with the chemo- and regioselective *N*-alkylation of a β-aminoalcohol, either as a single enantiomer (*R* or *S*) or its racemate, for example, *(R)*-2-amino-1-propanol, onto a 3,4-dihalonitrobenzene, for example, 3,4-difluoronitrobenzene, mediated by a base, for example, sodium bicarbonate, affords an optically pure arylamino alcohol (e.g., Structure **36**). Treatment of amino alcohol compounds such as Structure **36** with an aldehyde or the corresponding hydrate or hemiacetal, for example, trifluoroacetaldehyde ethyl hemiacetal, in the presence of an acid catalyst, for example *p*-toluenesulfonic acid, affords an optically pure oxazolidine compound (e.g., Structure **37**). Treatment of an oxazolidine compound such as Structure **37** with a reducing agent, for example, triethylsilane, in the presence of an acid, for example, boron trifluoride etherate, affords an N-alkyl substituted amino alcohol compound (e.g., Structure **38**). Benzoxazine compounds (e.g., Structure **39**), may then be formed by cyclization of the *N*-alkyl substituted amino alcohol compounds (e.g.,

Structure **38**) by treatment with a base such as sodium hydride. Reduction of nitro benzoxazine compounds (e.g., Structure **39**) with a reducing agent, for example, zinc and calcium chloride affords an amino benzoxazine compound (e.g., Structure **40**). Treatment of an amino benzoxazine with a β-ketoester or its corresponding hydrate, for example ethyl 4,4,4-trifluoroacetoacetate, at elevated temperatures, affords the corresponding acetanilide. Treatment of the acetanilide with an acid, for example, sulfuric acid, affords an optically pure quinolinone compound (e.g., Structure **41**). An enantiomer of Structure **41**, or a racemic mixture may be obtained by the synthetic route as described in **Scheme VIII**, by starting with the enantiomer of the β-aminoalcohol as shown (e.g., an (*S*)-β-amino alcohol), or a racemic mixture of the β-aminoalcohol shown (e.g., a (±)-β-amino alcohol. Accordingly, an (*S*)-β-amino alcohol, employed in **Scheme VII**, produces an (*S*)-quinolinone, an (*R*)-β-amino alcohol, employed in **Scheme VII**, produces an (*R*)-quinolinone, and a racemic mixture of the β-amino alcohol, employed in **Scheme VII**, produces a racemic mixture of the corresponding quinolinone.

Introduction of an *N*-alkyl or *N*-methylaryl group through the reductive cleavage of oxazolidine **37**, as outlined in **Scheme VIII**, is generally applicable to the preparation of enantiomerically pure arylamino alcohol compounds such as Structure **38**. Furthermore, the introduction of an *N*-(2-haloethyl) group through the reductive cleavage of an aryl oxazolidine is a novel process that has general utility in organic synthesis.

Preparation of *N*-Alkyl or *N*-Methylaryl Arylamino Alcohols



In the above process sequence, R^{4-7} may optionally represent hydrogen or alkyl or aryl groups, including $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl and wherein the

alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl are optionally substituted with halogen, $C_1 - C_4$ alkyl, or $C_1 - C_4$ haloalkyl;

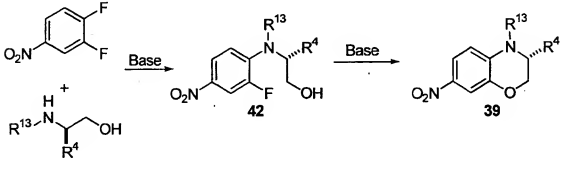
R^X may represent $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, allyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, allyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl are optionally substituted with halogen, $C_1 - C_4$ alkyl, or $C_1 - C_4$ haloalkyl.

Ar represents optionally substituted aryl or heteroaryl groups, including mono- and polycyclic structures, optionally substituted at one or more positions.

Additional substitutions are also possible and can be readily determined by one skilled in the art.

The above process sequence begins with an arylamino alcohol which is then converted into an oxazolidine with an aldehyde or the corresponding hydrate or hemiacetal in the presence of an acid catalyst. The oxazolidine is then converted to an *N*-alkylarylamino alcohol by addition of a reducing agent such as triethylsilane or sodium cyanoborohydride in the presence of a Lewis acid such as boron trifluoride etherate or a protic acid such as trifluoroacetic acid as a catalyst. Additional aldehydes and their corresponding hydrates as well as reducing agents may be used and are readily determined by those skilled in the art.

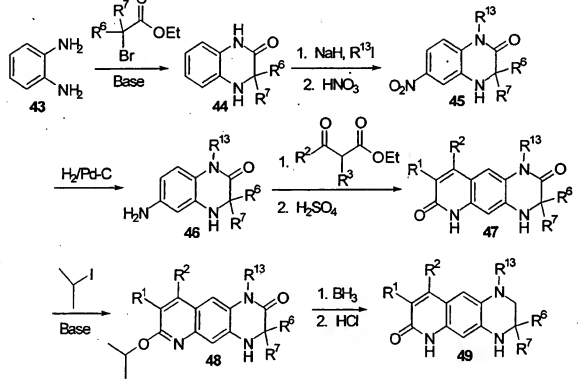
Scheme IX



Scheme IX describes an alternative to the route of **Scheme VIII** for formation of enantiomerically pure benzoxazine compounds such as Structure **39**. The route of

Scheme IX offers direct access to compounds of Structure **39** in which R^4 and R^{13} taken together form a ring structure. The process of **Scheme IX** begins with reaction of a secondary aminoalcohol, either a single enantiomer (*R* or *S*) or its racemate, for example 2-piperidinemethanol, with a 3,4-dihalonitrobenzene, for example, 3,4-difluoronitrobenzene, to afford an *N*-aryl substituted tertiary aminoalcohol compound such as Structure **42**. Cyclization of Structure **42**, mediated by treatment with a base, for example, sodium hydride, affords a benzoxazine compound (e.g., Structure **39**). Benzoxazine compounds such as Structure **39** may then further be employed in the synthesis of quinolinone compounds as described herein.

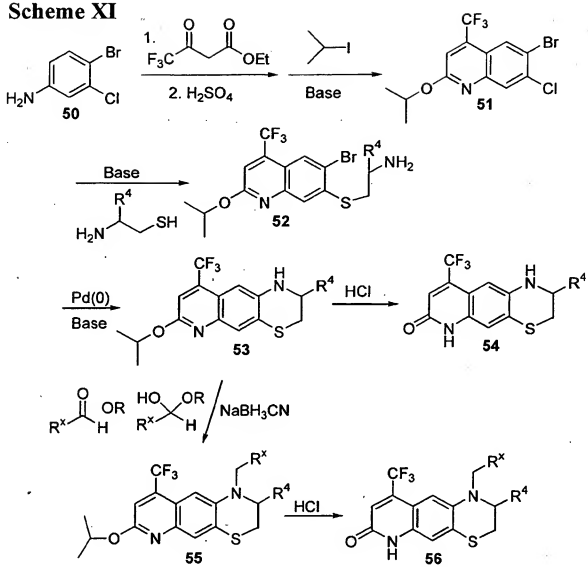
Scheme X



Pyrazino-quinolinone compounds (e.g., Structure **49**) may be prepared by the process described in **Scheme X**. The process of **Scheme X** begins with the alkylation of a 1,2-phenylenediamine, for example, 1,2-phenylenediamine, with an α-haloester, for example ethyl 2-bromoisobutyrate, mediated by a base, for example diisopropylethylamine, to afford a compound of Structure **44**. Nitration of **44** with, for example, nitric acid in sulfuric acid, affords a compound of Structure **45**. The nitro group

of **45** can be reduced to the corresponding aniline, with, for example, palladium on carbon under a hydrogen atmosphere, to afford a compound of Structure **46**. Treatment of the aniline with a β-ketoester or its corresponding hydrate, for example 4,4,4-trifluoroacetoacetate, at elevated temperatures, affords the corresponding acetanilide. Treatment of the acetanilide with an acid, for example, sulfuric acid, affords a compound of Structure **47**. Protection of the pyridone ring, with, for example isopropyl iodide mediated by a base, for example, cesium fluoride, affords the corresponding imino ether (Structure **48**). Reduction of the amide with, for example, borane dimethyl sulfide, affords the corresponding amine. Hydrolysis of this imino ether with an acid, for example, hydrochloric acid in acetic acid, affords a pyrazino-quinolinone compound such as Structure **49**.

Scheme XI



Thiazino-quinolinone compounds (e.g., Structure **56**) are prepared as shown in **Scheme XI**. The process of **Scheme XI** begins with the treatment of an aniline, for example, 4-bromo-3-chloroaniline, with a β-ketoester or its corresponding hydrate, for example 4,4,4-trifluoroacetoacetate, at elevated temperatures, to afford the corresponding acetanilide. Treatment of the acetanilide with an acid, for example, sulfuric acid, affords the corresponding 1*H*-quinolin-2-one (an example of a Knorr cyclization as described further herein). Protection of the pyridone ring, with, for example, isopropyl iodide, mediated by a base, for example, cesium fluoride, affords a compound of Structure **51**. Treatment of a compound (e.g., Structure **51**) with a β-aminothiol, for example, 2-

aminoethanethiol hydrochloride, mediated by a base, for example, sodium hydride, affords a compound of Structure **52**. Treatment of a compound of Structure **52** with a ligated transition metal, for example palladium acetate and BINAP, in the presence of a base, for example sodium *t*-butoxide, at elevated temperatures, affords a compound of Structure **53**. See S. Wagaw, *et al.*, *J. Am. Chem. Soc.* **1997**, *119*, 8451-8458. Treatment of a compound of Structure **53** with an aldehyde or its corresponding hydrate or hemiacetal, for example, formaldehyde, affords a compound of Structure **55**. Hydrolysis of the imino ether can be accomplished by treatment of a compound of Structure **55** with an acid, for example hydrochloric acid, at elevated temperatures, to afford a thiazino-quinolinone compound such as Structure **56**. Alternatively, a compound of Structure **53** can be deprotected with an acid, for example hydrochloric acid, at elevated temperatures, to afford a thiazino-quinolinone compound such as Structure **54**.

The compounds of the present invention also include racemates, stereoisomers and mixtures of said compounds, including isotopically-labeled and radio-labeled compounds. Such isomers can be isolated by standard resolution techniques, including fractional crystallization and chiral column chromatography.

As noted above, any of the steroid modulator compounds of the present invention can be combined in a mixture with a pharmaceutically acceptable carrier to provide pharmaceutical compositions useful for treating the biological conditions or disorders noted herein in mammalian, and more preferably, in human patients. The particular carrier employed in these pharmaceutical compositions may take a wide variety of forms depending upon the type of administration desired, e.g., intravenous, oral, topical, suppository or parenteral.

In preparing the compositions in oral liquid dosage forms (e.g., suspensions, elixirs and solutions), typical pharmaceutical media, such as water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like can be employed. Similarly, when preparing oral solid dosage forms (e.g., powders, tablets and capsules), carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like will be employed. Due to their ease of administration, tablets and capsules represent the most advantageous oral dosage form for the pharmaceutical compositions of the present invention.

For parenteral administration, the carrier will typically comprise sterile water, although other ingredients that aid in solubility or serve as preservatives, may also be included. Furthermore, injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents and the like will be employed.

For topical administration, the compounds of the present invention may be formulated using bland, moisturizing bases, such as ointments or creams. Examples of suitable ointment bases are petrolatum, petrolatum plus volatile silicones, lanolin, and water in oil emulsions such as Eucerin™ (Beiersdorf). Examples of suitable cream bases are Nivea™ Cream (Beiersdorf), cold cream (USP), Purpose Cream™ (Johnson & Johnson), hydrophilic ointment (USP), and Lubriderm™ (Warner-Lambert).

The pharmaceutical compositions and compounds of the present invention will generally be administered in the form of a dosage unit (e.g., tablet, capsule etc.) at from about 1 μg/kg of body weight to about 500 mg/kg of body weight, more preferably from about 10 μg/kg to about 250 mg/kg, and most preferably from about 20 μg/kg to about 100 mg/kg. As recognized by those skilled in the art, the particular quantity of pharmaceutical composition according to the present invention administered to a patient will depend upon a number of factors, including, without limitation, the biological activity desired, the condition of the patient, and tolerance for the drug.

The compounds of this invention also have utility when radio- or isotopically-labeled as ligands for use in assays to determine the presence of AR in a cell background or extract. They are particularly useful due to their ability to selectively activate androgen receptors, and can therefore be used to determine the presence of such receptors in the presence of other steroid receptors or related intracellular receptors.

Due to the selective specificity of the compounds of this invention for steroid receptors, these compounds can be used to purify samples of steroid receptors *in vitro*. Such purification can be carried out by mixing samples containing steroid receptors with one or more of the compounds of the present invention so that the compounds bind to the receptors of choice, and then separating out the bound ligand/receptor combination by separation techniques which are known to those of skill in the art. These techniques include column separation, filtration, centrifugation, tagging and physical separation, and antibody complexing, among others.

The compounds and pharmaceutical compositions of the present invention can advantageously be used in the treatment of the diseases and conditions described herein. In this regard, the compounds and compositions of the present invention will prove particularly useful as modulators of male sex steroid-dependent diseases and conditions such as the treatment of acne, male-pattern baldness, male hormone replacement therapy, sexual dysfunction, wasting diseases, hirsutism, stimulation of hematopoiesis, hypogonadism, prostatic hyperplasia, osteoporosis, male contraception, impotence, cancer cachexia, various hormone-dependent cancers, including, without limitation, prostate and breast cancer and as anabolic agents.

The compounds and pharmaceutical compositions of the present invention possess a number of advantages over previously identified steroidal and non-steroidal compounds.

Furthermore, the compounds and pharmaceutical compositions of the present invention possess a number of advantages over previously identified steroid modulator compounds. For example, the compounds are extremely potent activators of AR, preferably displaying 50% maximal activation of AR at a concentration of less than 100 nM, more preferably at a concentration of less than 50 nM, more preferably yet at a concentration of less than 20 nM, and most preferably at a concentration of 10 nM or less. Also, the selective compounds of the present invention generally do not display undesired cross-reactivity with other steroid receptors, as is seen with the compound mifepristone (RU486; Roussel Uclaf), a known PR antagonist that displays an undesirable cross reactivity on GR and AR, thereby limiting its use in long-term, chronic administration. In addition, the compounds of the present invention, as small organic molecules, are easier to synthesize, provide greater stability and can be more easily administered in oral dosage forms than other known steroidal compounds.

The invention will be further illustrated by reference to the following non-limiting Examples.

EXAMPLE 1

1,2,3,6-Tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **101**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = H).

General Method 1: Cyclization of an α-chloroacetyl chloride to 2-amino-5-nitrophenol. To a solution of 2-amino-5-nitrophenol (1.0 equiv), $NaHCO_3$ (2.4 equiv) in 4-methyl-2-pentanone (0.6 mL/mmol) and water (0.6 mL/mmol) was added an α-chloroacetyl chloride derivative (1.15 equiv) via syringe pump over 45 min at 0 °C. The reaction mixture was allowed to warm to room temperature and then refluxed overnight. The crude reaction mixture was allowed to cool to room temperature, filtered and washed with water (3 x 1.2 mL/mmol) to afford the desired product as a tan solid.

7-Nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (Structure **2** of **Scheme I**, where R^6 = H). This compound was prepared by General Method 1 from 2-amino-5-nitrophenol (6.0 g, 39 mmol), $NaHCO_3$ (7.8 g, 93 mmol), and chloroacetyl chloride (3.58 mL, 45 mmol) to afford 6.91 g (91%) of 7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one. Data for 7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one: R_f 0.44 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.31 (br s, 1H), 7.90 (dd, 1H, *J* = 8.7, 2.6), 7.76 (d, 1H, *J* = 2.5), 7.06 (d, 1H, *J* = 8.7), 4.73 (s, 2H).

General Method 2: Reduction of an amide Structure **2** to an amine of Structure **3**. To a solution of a 2*H*-1,4-benzoxazin-3(4*H*)-one of Structure **2** (1.0 equiv) in THF (10 mL/mmol) was added borane dimethylsulfide (2.0 M or 10.0 M in THF, 4 equiv) at rt, then the solution was heated to reflux for 16-18 hrs. The mixture was cooled to room temperature, quenched slowly with methanol until gas evolution stops, then refluxed for an additional 30 min. The solvent was removed under reduced pressure and the compound purified by flash chromatography as indicated.

3,4-Dihydro-7-nitro-2*H*-1,4-benzoxazine (Structure **3** of **Scheme I**, where R^6 = H). This compound was prepared by General Method 2 from 7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (2.0 g, 10 mmol) and borane dimethylsulfide (2.0 M in THF, 24 mL, 48

mmol) and purified on silica gel (20:1 CH_2Cl_2:MeOH) to afford 1.84 g (98%) of 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine, an orange solid. Data for 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine: R_f 0.76 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.74 (dd, 1H, *J* = 8.7, 2.5), 7.69 (d, 1H, *J* = 2.5), 6.52 (d, 1H, *J* = 8.7), 4.56 (br s, 1H), 4.26 (t, 2H, *J* = 4.4), 3.54 (td, 2H, *J* = 4.4, 2.5)

General Method 3: Reductive amination of a 3,4-dihydro-2*H*-1,4-benzoxazine derivative with sodium cyanoborohydride in acetic acid. To a solution of a 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (1.0 equiv) in acetic acid (7.8 mL/mmol) was added an aldehyde component (10 equiv) and the mixture was stirred at rt for 1h. To this mixture was added portionwise sodium cyanoborohydride (4.8 equiv) and stirred at room temperature overnight. The resulting mixture was poured over ice and neutralized with 6M NaOH to pH 7.0, extracted with CH_2Cl_2 (3 X 30 mL/mmol), washed with pH 7 phosphate buffer (50 mL/mmol) and brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to afford the desired product as a yellow solid.

3,4-Dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine (Structure 4 of Scheme I, where R^6 = H, R^x = H). This compound was prepared by General Method 3 from 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (1.15 g, 6.38 mmol), paraformaldehyde (1.92 g, 64.1 mmol) and $NaBH_3CN$ (1.95 g, 30.9 mmol) to afford 1.21 g (98%) of 3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine, a yellow solid. Data for 3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine: R_f 0.83 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, CDCl3) δ 7.82 (dd, 1H, *J* = 9.0, 2.6), 7.65 (d, 1H, *J* = 3.4), 6.56 (d, 1H, *J* = 8.9), 4.27 (t, 2H, *J* = 4.6), 3.46 (t, 2H, *J* = 4.5), 3.05 (s, 3H).

General Method 4: Hydrogenation of a 4-alkyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine. To a solution of a 4-alkyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine in 1:1 EtOAc:EtOH (13 mL/mmol) was added 10% Pd-C (6% by wt). The flask was flushed and evacuated with N_2 (3x), then stirred under an atmosphere of H_2 overnight. The reaction mixture was filtered through Celite, washed with EtOAc (2 X 20 mL/mmol) and

concentrated under reduced pressure to give the desired product as a light purple/tan solid, which was purified on silica gel as indicated.

7-Amino-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine. (Structure **5** of **Scheme I**, where R^6 = H, R^x = H). This compound was prepared by General Method 4 from 3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine (262 mg, 1.35 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 167 mg (75%) of 7-amino-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine. Data for 7-amino-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine: R_f 0.36 (11.5:1 CH_2Cl_2:MeOH) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.55 (d, 1H, *J* = 8.2), 6.25 (d, 1H, *J* = 2.6), 6.22 (dd, 1H, *J* = 7.0, 2.7), 4.28 (t, 2H, *J* = 4.4), 3.32 (br s, 2H), 3.13 (t, 2H, *J* = 4.5), 2.79 (s, 3H).

General Method 5: Condensation of a 7-amino-3,4-dihydro-2*H*-1,4-benzoxazine with acetoacetates or their corresponding hydrates followed by Knorr reaction mediated by polyphosphoric acid. To a solution of a 7-amino-3,4-dihydro-2*H*-1,4-benzoxazine of Structure **5** (1.0 equiv) in benzene (10 mL/mmol) under N_2 at room temperature was added an acetoacetate derivative (1.2 equiv) and the reaction was heated at reflux for 12-16 hrs, whereupon the mixture was concentrated under reduced pressure. The crude reaction mixture was diluted in polyphosphoric acid (8 mL/mmol) and heated to 100 °C for 12-16 hrs. The resulting mixture was poured over ice and neutralized with 6M NaOH solution to pH 7.0, extracted with CH_2Cl_2 (3 X 30 mL/mmol), washed with pH 7 phosphate buffer (50 mL/mmol) and brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 20:1, CH_2Cl_2/MeOH) afforded the desired quinolone as a fluorescent-yellow solid.

1,2,3,6-Tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **101**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^x = H). This compound was prepared by General Method 5 from 7-amino-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine (162 mg, 0.98 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.19 mL, 1.28 mmol) and purified by flash chromatography (19:1

CH_2Cl_2:MeOH) to afford 125 mg (44%) of Compound **101**. Data for Compound **101**: R_f 0.44 (EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.65 (br s, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 6.72 (s, 1H), 4.39 (t, 2H, J = 4.6), 3.31 (t, 2H, J = 4.5), 2.94 (s, 3H).

EXAMPLE 2

1,2,3,6-Tetrahydro-1,6-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **102**, Structure **7** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = H).

General Method 6: N-Methylation of a pyridone (compounds of Structure **6**) to form a compound of Structure **7**. To an oven-dried rb flask containing a pyridone of Structure **6** (1.0 equiv) in THF (5 mL/mmol) was added portionwise sodium hydride (60% dispersion in mineral oil, 1.2 equiv) under N_2. After 30 min, iodomethane (1.2 equiv) was added and the mixture was allowed to stir under N_2 an additional 8-10 hrs. The reaction mixture was then diluted with pH 7 phosphate buffer (50 mL/mmol), extracted with CH_2Cl_2 (3 X 30 mL) and washed with brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 20:1, CH_2Cl_2:MeOH) afforded the desired product as a fluorescent-yellow solid.

1,2,3,6-Tetrahydro-1,6-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **102**, Structure **7** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = H). This compound was prepared by General Method 6 from 3,4-dihydro-4-methyl-6-(trifluoromethyl)-8-pyridono-[5,6-*g*]-2*H*-1,4-benzoxazine (23.9 mg, 0.08 mmol), iodomethane (6.3 μL, 0.10 mmol) and sodium hydride (4.0 mg, 0.10 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 13.7 mg (55%) of Compound **102**. Data for Compound **102**: R_f 0.54 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.96 (s, 1H), 6.95 (s, 1H), 6.93 (s, 1H), 4.42 (t, 2H, J = 4.4), 3.66 (s, 3H), 3.31 (t, 2H, J = 4.6), 2.95 (s, 3H).

EXAMPLE 3

1-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **103**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^x = CH_3).

4-Ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = H, R^x = CH_3). This compound was prepared by General Method 3 (EXAMPLE 1) from 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (EXAMPLE 1) (1.15 g, 6.39 mmol), acetaldehyde (3.59 mL, 64.2 mmol) and $NaBH_3CN$ (1.95 g, 31 mmol) to afford 984 mg (74%) of 4-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine, a yellow solid. Data for 4-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine: R_f 0.85 (11.5:1 CH_2Cl_2:MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 9.6, 2.6), 7.66 (d, 1H, *J* = 2.7), 6.29 (d, 1H, *J* = 9.2), 4.23 (t, 2H, *J* = 4.7), 3.47 (t, 2H, *J* = 4.7), 3.45 (q, 2H, *J* = 7.2), 1.22 (t, 3H, *J* = 7.0).

7-Amino-4-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = H, R^x = CH_3). This compound was prepared by General Method 4 (EXAMPLE 1) from 4-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (264 mg, 1.3 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 173 mg (77%) of 7-amino-4-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine. Data for 7-amino-4-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine: R_f 0.52 (11.5:1 CH_2Cl_2:MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.56 (d, 1H, *J* = 8.1), 6.26-6.22 (m, 2H), 4.23 (t, 2H, *J* = 4.4), 3.29 (br s, 2H), 3.24 (q, 2H, *J* = 7.1), 3.19 (t, 2H, *J* = 4.4), 1.11 (t, 3H, *J* = 7.0).

1-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **103**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^x = CH_3). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-4-ethyl-3,4-dihydro-2*H*-1,4-benzoxazine (170 mg, 0.95 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.16 mL, 1.14 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 100 mg (35%) of Compound **103**. Data for Compound **103**:

R_f 0.21 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.47 (br s, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.81 (s, 1H), 4.35 (t, 2H, *J* = 4.5), 3.4 (q, 2H, *J* = 7.1), 3.34 (t, 2H, *J* = 4.5), 1.19 (t, 3H, *J* = 7.1). Anal. Calcd for $C_{14}H_{13}F_3N_2O_2$: C, 56.38; H, 4.39; N, 9.39. Found: C, 56.04; H, 4.32; N, 9.22.

EXAMPLE 4

1-Ethyl-1,2,3,6-tetrahydro-6-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **104**, Structure **7 of Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = CH_3). This compound was prepared by General Method 6 (EXAMPLE 2) from Compound **103** (18.5 mg, 0.06 mmol), iodomethane (5.8 μL, 0.09 mmol) and sodium hydride (3.6 mg, 0.09 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 13.5 mg (71%) of Compound **104**. Data for Compound **104**: R_f 0.57 (2:3 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.98 (s, 1H), 6.93 (s, 1H), 6.85 (s, 1H), 4.38 (t, 2H, *J* = 4.5), 3.66 (s, 3H), 3.4 (q, 2H, *J* = 7.1), 3.35 (t, 2H, *J* = 4.6), 1.19 (t, 3H, *J* = 7.1).

EXAMPLE 5

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **105**, Structure **6 of Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = CF_3).

General Method 7: Reductive amination of a 7-nitro-2*H*-1,4-benzoxazine in trifluoroacetic acid. To a solution of a 7-nitro-3,4-dihydro-2*H*-1,4-benzoxazine (1.0 equiv) in trifluoroacetic acid (0.5 mL/mmol) was added an aldehyde or its corresponding hydrate (10 equiv) and the mixture was stirred at rt for 2 h. To this mixture was added portionwise sodium cyanoborohydride (4.8 equiv) and stirred at room temperature overnight. The resulting mixture was poured over ice and neutralized with 6M NaOH solution to pH 7.0, extracted with CH_2Cl_2 (3 X 30 mL/mmol), washed with pH 7 phosphate buffer (50 mL/mmol) and brine (50 mL/mmol). The organic solution was dried

($MgSO_4$) and concentrated under reduced pressure to afford the desired product as a yellow solid.

3,4-Dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = H, R^x = CF_3). This compound was prepared by General Method 7 from 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (EXAMPLE 1) (388 mg, 2.1 mmol), 2,2,2-trifluoroacetaldehyde monohydrate (2.51 g, 21.6 mmol) and $NaBH_3CN$ (656 mg, 10.4 mmol) to afford 500 mg (88%) of 3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine, a yellow solid. Data for 3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.59 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 8.8, 2.6), 7.72 (d, 1H, *J* = 2.6), 6.72 (d, 1H, *J* = 9.1), 4.27 (t, 2H, *J* = 4.5), 3.94 (q, 2H, *J* = 8.6), 3.61 (t, 2H, *J* = 4.5).

7-Amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = H, R^x = CF_3). This compound was prepared by General Method 4 (EXAMPLE 1) from 3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (3.12 g, 12 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 2.7 g (98%) of 7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine. Data for 7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.47 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.56 (d, 1H, *J* = 8.2), 6.30-6.20 (m, 2H), 4.16 (t, 2H, *J* = 4.3), 3.65 (q, 2H, *J* = 9.1), 3.39 (t, 2H, *J* = 4.4), 3.36 (br s, 1H).

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **105**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^x = CF_3). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (2.7 g, 11.6 mmol), and ethyl 4,4,4-trifluoroacetoacetate (2.04 mL, 14 mmol) and purified by flash chromatography (3:2 EtOAc:hexanes) and recrystallized from MeOH to afford 790 mg (19 %) of Compound **105**. Data for Compound **105**: R_f 0.25 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.95 (br s, 1H), 7.04 (br s, 1H), 6.91

(s, 1H), 6.90 (s, 1H), 4.33 (t, 2H, J = 4.5), 3.88 (q, 2H, J = 8.9), 3.56 (t, 2H, J = 4.5). Anal. Calcd for $C_{14}H_{10}F_6N_2O_2$: C, 47.74; H, 2.86; N, 7.95. Found: C, 47.81; H, 2.80; N, 7.87.

EXAMPLE 6

8-Fluoro-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **106**, Structure **6** of **Scheme I**, where R^1 = F, R^2 = trifluoromethyl, R^6 = H, R^x = CF_3). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (EXAMPLE 5) (24 mg, 0.1 mmol), and ethyl 2,4,4,4-tetrafluoro-3,3-dihydroxybutanoate (27 mg, 0.12 mmol) and purified by flash chromatography (1:1 EtOAc:hexanes) to afford 8 mg (21%) of Compound **106**. Data for Compound **106**: R_f 0.15 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.38 (br s, 1H), 7.08 (s, 1H), 6.86 (s, 1H), 4.32 (t, 2H, J = 4.5), 3.88 (q, 2H, J = 8.8), 3.56 (t, 2H, J = 4.4)

EXAMPLE 7

8-Chloro-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **107**, Structure **6** of **Scheme I**, where R^1 = Cl, R^2 = trifluoromethyl, R^6 = H, R^x = CF_3). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (EXAMPLE 5) (21 mg, 0.1 mmol), and ethyl 2-chloro-4,4,4-trifluoroacetoacetate (23 mg, 0.1 mmol) and purified by reverse phase HPLC (ODS, 75:25 MeOH:water, 3 mL/min) to afford 2 mg (6%) of Compound **107**. Data for Compound **107**: R_f 0.12 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.22 (br s, 1H), 7.15 (s, 1H), 6.75 (s, 1H), 4.33 (t, 2H, J = 4.5), 3.87 (q, 2H, J = 8.7), 3.56 (t, 2H, J = 4.4).

EXAMPLE 8

9-(Difluoromethyl)-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **108**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = difluoromethyl, R^6 = H, R^x = CF_3). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (EXAMPLE 5) (310 mg, 1.3 mmol), and ethyl 4,4-difluoroacetoacetate (243 mg, 1.5 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 50 mg (11 %) of Compound **108**. Data for Compound **108**: R_f 0.22 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) 10.92 (br s, 1H), 7.06 (s, 1H), 6.82 (s, 1H), 6.72 (t, 1H, J = 54.2), 6.71 (s, 1H), 4.32 (t, 2H, J = 4.4), 3.85 (q, 2H, J = 8.9), 3.54 (t, 2H, J = 4.4).

EXAMPLE 9

1,2,3,6-Tetrahydro-6-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **109**, Structure **7** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^x = CF_3). This compound was prepared by General Method 6 (EXAMPLE 2) from Compound **105** (EXAMPLE 5) (85.0 mg, 0.24 mmol), iodomethane (18 µL, 0.29 mmol) and sodium hydride (11.6 mg, 0.29 mmol) and purified by flash chromatography (3:2 EtOAc:hexanes) to afford 73 mg (83%) of Compound **109**. Data for Compound **109**: R_f 0.47 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) 7.09 (s, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 4.36 (t, 2H, *J* = 4.4), 3.88 (q, 2H, J = 8.9), 3.66 (s, 3H), 3.57 (t, 2H, J = 4.4).

EXAMPLE 9A

7-Chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-g]quinoline (Compound **109A**, Structure **7A** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, $R^X = CF_3$, R^A = Cl). A solution of Compound **105** (EXAMPLE 5) (25 mg, 0.07 mmol) in 3 mL $POCl_3$ was heated at 80 °C for 2 h. The reaction was quenched with $NaHCO_3$ (sat'd) in ice and neutralized to pH = 7. The mixture was extracted with CH_2Cl_2, and the organic layers were washed with brine, dried over MgSO4, filtered, and concentrated. Flash chromatography (95:5 CH_2Cl_2:MeOH) afforded 20 mg (77%) of Compound **109A**, a yellow solid. Data for Compound **109A**: ^{1}H NMR (400 MHz, $CDCl_3$) 7.48 (s, 1H), 7.46 (s, 1H), 7.16 (s, 1H), 4.38 (t, 2H, *J* = 4.6), 4.00 (q, 2H, J = 8.8), 3.66 (t, 2H, J = 4.4).

EXAMPLE 10

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-thione (Compound **110**, Structure **8** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, $R^X = CF_3$).

General Method 8: Conversion of a pyridone to a thiopyridone. To a solution of a pyridone of Structure **6** (1.0 equiv) in benzene (0.6 mL/mmol) was added Lawesson's reagent (1.0 equiv) and heated to 60 °C for 12-16 hours. The reaction mixture was allowed to cool to room temperature, partitioned with H_2O/ether (200 mL/100 mL), extracted with ether (2 X 30 mL), and washed with brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure to give the desired product as an orange solid, which was purified on silica gel as indicated.

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-thione (Compound **110**, Structure **8** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, $R^X = CF_3$). This compound was prepared by General Method 8 from Compound **105** (EXAMPLE 5) (50.0 mg, 0.15 mmol) and Lawesson's reagent (57.0 mg, 0.15 mmol) and purified by flash chromatography (19:1

CH_2Cl_2:MeOH) to afford 12 mg (23%) of Compound **110**. Data for Compound **110**: ^{1}**H NMR** (400 MHz, $CDCl_3$) 11.47 (br s, 1H), 7.04 (s, 2H), 6.91 (s, 1H), 4.35 (t, 2H, J = 4.6), 3.97 (q, 2H, J = 8.8), 3.63 (t, 2H, J = 4.6).

EXAMPLE 11

1,2,3,6-Tetrahydro-1-propyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **111**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = CH_3CH_2).

7-Nitro-4-propyl-2*H*-1,4-benzoxazine (Structure 4 of **Scheme I**, where R^6 = H, R^X = CH_3CH_2). This compound was prepared by General Method 3 (EXAMPLE 1) from 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (EXAMPLE 1) (530 mg, 2.9 mmol), propionaldehyde (1.61 g, 28 mmol) and $NaBH_3CN$ (872 mg, 14 mmol) to afford 450 mg (69%) of 3,4-dihydro-7-nitro-4-propyl-2*H*-1,4-benzoxazine, an orange oil. Data for 3,4-dihydro-7-nitro-4-propyl-2*H*-1,4-benzoxazine: R_f 0.57 (2:1 EtOAc:hexanes); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.80 (dd, 1H, *J* = 9.1, 2.6), 7.66 (d, 1H, *J* = 2.6), 6.56 (d, 1H, *J* = 9.0), 4.22 (t, 2H, *J* = 4.5), 3.49 (t, 2H, *J* = 4.5), 3.33 (t, 2H, *J* = 7.5), 1.67 (sext, 2H, *J* = 7.4), 0.98 (t, 3H, *J* = 7.4).

7-Amino-3,4-dihydro-4-propyl-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = H, R^X = CH_3CH_2). This compound was prepared by General Method 4 (EXAMPLE 1) from 3,4-dihydro-7-nitro-4-propyl-2*H*-1,4-benzoxazine (50 mg, 0.2 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 36 mg (84%) of 7-amino-3,4-dihydro-4-propyl-2*H*-1,4-benzoxazine. Data for 7-amino-3,4-dihydro-4-propyl-2*H*-1,4-benzoxazine: R_f 0.43 (2:1 EtOAc:hexanes); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.53 (d, 1H, *J* = 8.9), 6.25-6.20 (m, 2H), 4.21 (t, 2H, *J* = 4.4), 3.28 (br s, 2H), 3.21 (t, 2H, *J* = 4.4), 3.08 (t, 2H, *J* = 7.5), 1.60 (sext, 2H, *J* = 7.4), 0.94 (t, 3H, *J* = 7.4).

1,2,3,6-Tetrahydro-1-propyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **111**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^x = CH_3CH_2). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-3,4-dihydro-4-propyl-2*H*-1,4-benzoxazine (395 mg, 2.0 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.36 mL, 2.5 mmol) and purified by flash chromatography (3:2 EtOAc:hexanes) and recrystallized from MeOH to afford 100 mg (16 %) of Compound **111**. Data for Compound **111**: R_f 0.24 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) 11.79 (br s, 1H), 6.88 (s, 1H), 6.87 (s, 1H), 6.83 (s, 1H), 4.32 (t, 2H, *J* = 4.5), 3.37 (t, 2H, *J* = 4.5), 3.26 (t, 2H, *J* = 7.4),1.66 (sext, 2H, J =7.4), 0.99 (t, 3H, *J* =7.4).

EXAMPLE 12

1,2,3,6-Tetrahydro-1-isobutyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **112**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^x = $(CH_3)_2CH$).

3,4-Dihydro-4-isobutyl-7-nitro-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = H, R^x = $(CH_3)_2CH$). This compound was prepared by General Method 3 (EXAMPLE 1) from 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (EXAMPLE 1) (550 mg, 3.0 mmol), isobutyraldehyde (1.65 g, 22.8 mmol) and $NaBH_3CN$ (959 mg, 15 mmol) to afford 713 mg (99%) of 3,4-dihydro-4-isobutyl-7-nitro-2*H*-1,4-benzoxazine, an yellow solid. Data for 3,4-dihydro-4-isobutyl-7-nitro-2*H*-1,4-benzoxazine: R_f 0.75 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dd, 1H, *J* = 9.0, 2.6), 7.66 (d, 1H, *J* = 2.6), 6.55 (d, 1H, *J* = 9.2), 4.21 (t, 2H, *J* = 4.5), 3.52 (t, 2H, *J* = 4.6), 3.16 (d, 2H, *J* = 7.4), 3.12 (hept, 1H, *J* = 6.9), 0.97 (d, 6H, *J* = 6.7).

7-Amino-3,4-dihydro-4-isobutyl-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = H, R^x = $(CH_3)_2CH$). This compound was prepared by General Method 4 (EXAMPLE 1) from 3,4-dihydro-4-isobutyl-7-nitro-2*H*-1,4-benzoxazine (712 mg, 3.0

mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 621 mg (99%) of 7-amino-4-isobutyl-2*H*-1,4-benzoxazine. Data for 7-amino-3,4-dihydro-4-isobutyl-2*H*-1,4-benzoxazine: R_f 0.43 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.49 (d, 1H, *J* = 9.1), 6.23 (m, 2H), 4.20 (t, 2H, *J* = 4.4), 3.28 (br s, 2H), 3.23 (t, 2H, *J* = 4.4), 2.85 (d, 2H, *J* = 7.2), 2.04-1.92 (m, 1H), 0.94 (d, 6H, *J* = 6.5).

1,2,3,6-Tetrahydro-1-isobutyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **112**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = $(CH_3)_2CH$). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-3,4-dihydro-4-isobutyl-2*H*-1,4-benzoxazine (620 mg, 3.0 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.527 mL, 3.6 mmol) and purified by flash chromatography (3:2 EtOAc:hexanes) and recrystallized from MeOH to afford 241 mg (25 %) of Compound **112**. Data for Compound **112**: R_f 0.2 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.62 (br s, 1H), 6.87 (s, 2H), 6.74 (s, 1H), 4.31 (t, 2H, *J* = 4.5), 3.41 (t, 2H, *J* = 4.5), 3.05 (d, 2H, *J* = 7.0), 2.05-1.95 (m, 1H), 0.98 (d, 6H, J = 6.5).

EXAMPLE 13

1,2,3,6-Tetrahydro-1-isobutyl-6-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **113**, Structure **7** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = H, R^X = $(CH_3)_2CH$). This compound was prepared by General Method 6 (EXAMPLE 2) from Compound **112** (10.0 mg, 0.03 mmol), iodomethane (3.0 μL, 0.03 mmol) and sodium hydride (1.5 mg, 0.03 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 8.3 mg (80%) of Compound **113**. Data for Compound **113**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (s, 2H), 6.85 (s, 1H), 4.34 (t, 2H, *J* = 4.5), 3.65 (s, 3H), 3.43 (t, 2H, *J* = 4.5), 3.06 (d, 2H, *J* = 7.2), 2.09 (m, 1H), 0.99 (d, 6H, *J* = 6.6).

EXAMPLE 14

(±)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **114**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = CF_3).

(±)-2-Methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (Structure **2** of **Scheme I**, where R^6 = Me). This compound was prepared by General Method 1 (EXAMPLE 1) from 2-amino-5-nitrophenol (3.0 g, 20 mmol), $NaHCO_3$ (3.9 g, 46 mmol), and 2-chloropropionyl chloride (2.2 mL, 22 mmol) to afford 3.1 g (77%) of (±)-2-methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one. Data for (±)-2-methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one: R_f 0.45 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, DMSO) δ 11.28 (br s, 1H), 7.92 (dd, 1H, *J* = 8.6, 2.2), 7.77 (d, 1H, *J* = 2.6), 7.07 (d, 1H, *J* = 8.7), 4.85 (q, 1H, *J* = 6.7), 1.46 (d, 3H, *J* = 6.8).

(±)-3,4-Dihydro-2-methyl-7-nitro-2*H*-1,4-benzoxazine (Structure **3** of **Scheme I**, where R^6 = Me). This compound was prepared by General Method 2 (EXAMPLE 1) from (±)-2-methyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (1.8 g, 8.6 mmol) and borane dimethylsulfide (10.0-10.2 M in THF, 3.5 mL, 35 mmol) and purified on silica gel (20:1 CH_2Cl_2:MeOH) to afford 1.57 g (94%) of 3,4-dihydro-2-methyl-7-nitro-2*H*-1,4-benzoxazine, an orange solid. Data for 3,4-dihydro-2-methyl-7-nitro-2*H*-1,4-benzoxazine: R_f 0.75 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, 1H, *J* = 8.7, 2.6), 7.69 (d, 1H, *J* = 2.2), 6.52 (d, 1H, 8.7), 4.56 (br s, 1H), 4.20 (m, 1H), 3.47 (ddd, 1H, *J* = 12.1, 3.8, 2.7), 3.21 (ddd, 1H, *J* = 12.0, 8.1, 1.2), 1.40 (d, 3H, *J* = 6.1).

(±)-3,4-Dihydro-2-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = Me, R^x = CF_3). This compound was prepared by General Method 7 (EXAMPLE 5) from (±)-3,4-dihydro-2-methyl-7-nitro-2*H*-1,4-benzoxazine (400 mg, 2.0 mmol), 2,2,2-trifluoroacetaldehyde monohydrate (2.4 g, 20.6 mmol) and $NaBH_3CN$ (628 mg, 10.0 mmol) to afford 550 mg (96%) of (±)-3,4-dihydro-2-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine, a yellow solid. Data for (±)-3,4-dihydro-2-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.85

(3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 9.2, 2.6), 7.72 (d, 1H, *J* = 2.6), 6.72 (d, 1H, J = 9.1), 4.23 (m, 1H), 4.23-3.82 (m, 2H), 3.47 (dd, 1H, *J* = 12.1, 2.6), 3.37 (dd, 1H, *J* = 12.2, 8.2), 1.41 (d, 3H, *J* = 6.1).

(±)-7-Amino-3,4-dihydro-2-methyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = Me, R^x = CF_3). This compound was prepared by General Method 4 (EXAMPLE 1) from (±)-3,4-dihydro-2-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (394 mg, 1.4 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 345 mg (98%) of (±)-7-amino-3,4-dihydro-2-methyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine. Data for (±)-7-amino-3,4-dihydro-2-methyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.60 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.57 (d, 1H, *J* = 9.2), 6.27-6.22 (m, 2H), 6.24 (s, 1H), 4.18 (m, 1H), 3.75-3.62 (m, 3H), 3.27 (dd, 1H, *J* = 12.0, 9.8), 3.10 (dd, 1H, *J* = 12.0, 8.5), 1.34 (d, 3H, *J* = 6.3).

(±)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **114**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = CF_3). This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-7-amino-3,4-dihydro-2-methyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (345 mg, 1.4 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.24 mL, 1.6 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 52 mg (34 %) of Compound **114**. Data for Compound **114**: R_f 0.26 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.84 (br s, 1H), 7.05 (s, 1H), 6.90 (s, 1H), 6.82 (s, 1H), 4.35 (m, 1H), 3.91 (m, 1H), 3.83 (m, 1H), 3.44 (dd, 1H, *J* = 12.1, 2.0), 3.21 (dd, 1H, *J* = 11.7, 7.8), 1.42 (d, 3H, *J* = 6.2). Anal. Calcd for $C_{15}H_{12}F_6N_2O_2$: C, 49.19; H, 3.30; N, 7.65. Found: C, 49.19; H, 3.23; N, 7.54.

EXAMPLE 15

(-)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **115**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = CF_3) and (+)-1,2,3,6-tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **116**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = CF_3).

General Method 9: Resolution of Compounds of Structure **6**, **18**, or **23** to their corresponding enantiomers via chiral HPLC. A preparative Chiralpak AD column (10 μm particle size, 20 x 250 mm OR 10 x 250 mm, Daicel Chemical Industries, Ltd.) on a Beckman Gold HPLC was equilibrated with an eluent of hexanes:isopropanol at a flow rate of 4.5-5 mL/min. A solution of the racemic compound in MeOH, EtOH, or acetone was prepared and injections were monitored to insure that baseline separation is achieved. Compound elution was monitored by absorbance detection at 254 nM. Sequential injections were performed until the specified amounts were obtained. The solvents of the separated enantiomers were removed *in vacuo*. Purity of the collected fractions were verified by injection of analytical amounts and in each case only a single enantiomer was detected.

(-)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **115**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = CF_3) and (+)-1,2,3,6-tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **116**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = CF_3).

This compound was prepared according to General Method 9 from Compound **114** (10 mg, 0.03 mmol) on a semiprep Chiralpak AD column (10 x 250 mm) and eluted with hexanes/isopropanol (95:5), to afford 3 mg of Compound **115**, a yellow solid, and 2.0 mg of Compound **116**, a yellow solid. Data for Compound **115**: HPLC (Chiralpak

AD, 4 x 250 mm, 95:5 hexanes:isopropanol, 0.8 mL/min) t_R 16.9 min; $[\alpha]_D$ = -78 (c = 0.18). Data for Compound **116**: HPLC (Chiralpak AD, 4 x 250 mm, 95:5 hexanes:isopropanol, 0.8 mL/min) t_R 20.0 min; $[\alpha]_D$ = +70 (c = 0.12).

EXAMPLE 16

(±)-1,2,3,6-Tetrahydro-1,3-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **117**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = H).

(±)-3,4-Dihydro-2,4-dimethyl-7-nitro-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = Me, R^x = H). This compound was prepared from General Method 3 (EXAMPLE 1) from (±)-3,4-dihydro-2-methyl-7-nitro-2*H*-1,4-benzoxazine (150 mg, 0.77 mmol), paraformaldehyde (233 mg, 7.8 mmol) and $NaBH_3CN$ (235 mg, 3.7 mmol) to afford 160 mg (99%) of (±)-3,4-dihydro-2,4-dimethyl-7-nitro-2*H*-1,4-benzoxazine. Data for (±)-3,4-dihydro-2,4-dimethyl-7-nitro-2*H*-1,4-benzoxazine: R_f 0.77 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 9.1, 2.5), 7.66 (d, 1H, *J* = 2.5), 6.55 (d, 1H, *J* = 8.9), 4.26-4.23 (m, 1H), 3.32 (dd, 1H, *J* = 12.1, 2.7), 3.22 (dd, 1H, *J* = 12.0, 8.2), 3.03 (s, 3H), 1.39 (d, 3H, *J* = 6.5).

(±)-7-Amino-3,4-dihydro-2,4-dimethyl-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = Me, R^x = H). This compound was prepared from General Method 4 EXAMPLE 1) from (±)-3,4-dihydro-2,4-dimethyl-7-nitro-2*H*-1,4-benzoxazine (160 mg, 0.77 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 134 mg (97%) of (±)-7-amino-3,4-dihydro-2,4-dimethyl-2*H*-1,4-benzoxazine. Data for (±)-7-amino-3,4-dihydro-2,4-dimethyl-2*H*-1,4-benzoxazine: R_f 0.35 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.54 (d, 1H, *J* = 8.0), 6.25-6.20 (m, 2H), 4.36-4.33 (m, 1H), 3.31 (br s, 2H), 3.08 (dd, 1H, *J* = 11.4, 2.3), 2.82 (dd, 1H, 11.4, 8.2), 2.78 (s, 3H), 1.33 (d, 3H, *J* = 6.2).

(±)-1,2,3,6-Tetrahydro-1,3-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **117**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Me, R^x = H). This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-7-amino-3,4-dihydro-2,4-dimethyl-2*H*-1,4-benzoxazine (75 mg, 0.42 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.07 mL, 0.48 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 50 mg (40%) of Compound **117**. Data for Compound **117**: R_f 0.42 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.17 (br s, 1H), 6.88 (s, 1H), 6.87 (s, 1H), 6.78 (s, 1H), 4.45 (m, 1H), 3.24 (dd, 1H, *J* = 11.7, 2.5), 3.02 (dd, 1H, *J* = 11.5, 8.2), 2.93 (s, 3H), 1.40 (d, 3H, *J* = 6.5).

EXAMPLE 17

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **118**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Et, R^x = CF_3).

(±)-2-Ethyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (Structure **2** of **Scheme I**, where R^6 = Et). This compound was prepared by General Method 1 (EXAMPLE 1) from 2-amino-5-nitrophenol (3.0 g, 19.5 mmol), $NaHCO_3$ (3.9 g, 46.5 mmol), and 2-chlorobutyryl chloride (3.1 g, 22.4 mmol) to afford 1.2 g (28%) of (±)-2-ethyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one. Data for (±)-2-ethyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one: R_f 0.48 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.29 (br s, 1H), 7.91 (dd, 1H, *J* = 8.7, 2.6), 7.79 (d, 1H, *J* = 2.4), 7.06 (d, 1H, *J* = 8.7), 4.71-4.68 (m, 1H), 1.88-1.76 (m, 2H), 1.00 (t, 3H, *J* = 7.2).

(±)-2-Ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (Structure **3** of **Scheme I**, where R^6 = Et). This compound was prepared by General Method 2 (EXAMPLE 1) from (±)-2-ethyl-7-nitro-2*H*-1,4-benzoxazin-3(4*H*)-one (1.2 g, 5.4 mmol) and borane dimethylsulfide (10.0-10.2 M in THF, 2.2 mL, 22 mmol) and purified on silica gel (1.8:1 hexanes:EtOAc) to afford 723 mg (65%) of (±)-2-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine, an orange solid. Data for (±)-2-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-

benzoxazine: R_f 0.85 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (dd, 1H, *J* = 8.5, 2.4), 7.71 (d, 1H, *J* = 2.3), 6.50 (d, 1H, *J* = 8.6), 4.53 (br s, 1H), 3.99-3.94 (m, 1H), 3.48 (dd, 1H, *J* = 8.9, 3.0), 3.23 (dd, 1H, *J* = 10.9, 8.0), 1.75-1.61 (m, 2H), 1.07 (t, 3H, *J* = 7.5).

(±)-2-Ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = Et, R^x = CF_3). This compound was prepared by General Method 7 (EXAMPLE 5) from (±)-2-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (250 mg, 1.2 mmol), 2,2,2-trifluoroacetaldehyde monohydrate (1.4 g, 12 mmol) and $NaBH_3CN$ (366 mg, 5.8 mmol) to afford 346 mg (99%) of (±)-2-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine. Data for (±)-2-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.75 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (dd, 1H, *J* = 8.9, 2.6), 7.73 (d, 1H, *J* = 2.5), 6.70 (d, 1H, *J* = 9.0), 4.03-3.81 (m, 3H), 3.48 (dd, 1H, *J* = 12.1, 2.6), 3.39 (dd, 1H, *J* = 12.1, 8.0), 1.80-1.62 (m, 2H), 1.08 (t, 3H, *J* = 7.4).

(±)-7-Amino-2-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = Et, R^x = CF_3). This compound was prepared by General Method 4 (EXAMPLE 1) from (±)-2-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (170 mg, 0.6 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 151 mg (99%) of (±)-7-amino-2-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine. Data for (±)-7-amino-2-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.62 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.56 (d, 1H, *J* = 8.0), 6.25-6.20 (m, 2H), 3.93 (m, 1H), 3.70-3.64 (m, 3H), 3.43 (br s, 1H), 3.31 (m, 1H), 3.12 (dd, 1H, *J* = 11.9, 8.1), 1.74-1.59 (m, 2H), 1.04 (t, 3H, *J* = 7.5).

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **118**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Et, R^x = CF_3). This compound was prepared by General

Method 5 (EXAMPLE 1) from (±)-7-amino-2-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (100 mg, 0.38 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.81 mg, 0.44 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 75 mg (51 %) of Compound **114**. Data for Compound **114**: R_f 0.18 (19:1 CH_2Cl_2:MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 12.05 (br s, 1H), 7.03 (s, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 4.15-4.05 (m, 1H), 3.98-3.88 (m, 1H), 3.88-3.75 (m, 1H), 3.44 (dd, 1H, *J* = 11.8, 2.5), 3.32 (dd, 1H, *J* = 11.9, 8.1), 1.76 (m, 1H), 1.68 (m, 1H), 1.09 (t, 3H, *J* = 7.6).

EXAMPLE 18

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **119**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Et, R^x = H).

(±)-2-Ethyl-3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = Et, R^x = H). This compound was prepared by General Method 3 (EXAMPLE 1) from 2-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (EXAMPLE 17) (120 mg, 0.57 mmol), paraformaldehyde (174 mg, 5.8 mmol) and $NaBH_3CN$ (176 mg, 2.8 mmol) to afford 127 mg (99%) of 2-ethyl-3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine. Data for 2-ethyl-3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine: R_f 0.89 (11.5:1 CH_2Cl_2:MeOH); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 9.0, 2.5), 7.67 (d, 1H, *J* = 2.5), 6.54 (d, 1H, *J* = 9.0), 4.01 (m, 1H), 3.34 (dd, 1H, *J* = 12.0, 2.7), 3.23 (dd, 1H, *J* = 12.0, 8.1), 3.03 (s, 3H), 1.79-1.72 (m, 1H), 1.67-1.60 (m, 1H), 1.07 (t, 3H, *J* = 7.5).

(±)-7-Amino-2-ethyl-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = Et, R^x = H). This compound was prepared by General Method 4 (EXAMPLE 1) from (±)-2-ethyl-3,4-dihydro-4-methyl-7-nitro-2*H*-1,4-benzoxazine (130 mg, 0.6 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to afford 80 mg (71%) of (±)-7-amino-2-ethyl-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine. Data for

(±)-7-amino-2-ethyl-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine: R_f 0.5 (19:1 CH_2Cl_2/MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.53 (dd, 1H, *J* = 9.1, 2.7), 6.25-6.20 (m, 2H), 4.11 (m, 1H), 3.10 (dd, 1H, *J* = 11.4, 2.1), 2.84 (dd, 1H, *J* = 11.3, 8.1), 2.78 (s, 3H), 1.75-1.70 (band, 1H), 1.64-1.58 (m, 1H), 1.03 (t, 2H, *J* = 7.5).

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **119**, Structure **6** of **Scheme I**, where R^1 = H, R^2 = trifluoromethyl, R^6 = Et, R^X = H). This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-7-amino-2-ethyl-3,4-dihydro-4-methyl-2*H*-1,4-benzoxazine (80 mg, 0.4 mmol), and ethyl 4,4,4-trifluoroacetoacetate (0.92 mg, 0.5 mmol) and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 26 mg (20 %) of Compound **119**. Data for Compound **119**: R_f 0.19 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.5 (br s, 1H), 6.89 (s, 2H), 6.83 (s, 1H), 4.22 (m, 1H), 3.26 (dd, 1H, *J* = 11.6, 2.4), 3.05 (dd, 1H, *J* = 11.6, 8.2), 2.94 (s, 3H), 1.76 (m, 1H), 1.67 (m, 1H), 1.08 (t, 3H, *J* = 7.5).

EXAMPLE 19

1,2,3,6-Tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **120**, Structure **10** of **Scheme II**, where R^1 = H, R^2 = trifluoromethyl).

3,4-Dihydro-4-(*p*-methoxybenzyl)-7-nitro-2*H*-1,4-benzoxazine (Structure **4** of **Scheme I**, where R^6 = H, R^X = 4-anisyl). This compound was prepared by General Method 3 (EXAMPLE 1) from 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (EXAMPLE 1) (305 mg, 1.7 mmol), *p*-anisaldehyde (2.3 g, 17 mmol) and $NaBH_3CN$ (532 mg, 8.4 mmol) to afford 361 mg (70%) of 3,4-dihydro-4-(*p*-methoxybenzyl)-7-nitro-2*H*-1,4-benzoxazine, an yellow solid. Data for 3,4-dihydro-4-(*p*-methoxybenzyl)-7-nitro-2*H*-1,4-benzoxazine: R_f 0.79 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, 1H, *J* = 9.0, 2.6), 7.70 (d, 1H, *J* = 2.5), 7.14 (d, 2H, *J* = 8.6), 6.88 (d, 2H, *J* = 8.6), 6.63 (d, 1H, *J* =9.1), 4.54 (s, 2H), 4.26 (t, 2H, *J* = 4.5), 3.80 (s, 3H), 3.51 (t, 2H, *J* = 4.6).

General Method 10: Reduction of a nitrobenzene derivative to an aniline with zinc/ calcium chloride dihydrate. To a solution of the nitrobenzene derivative (1.0 equiv) in ethanol:water (95:5) was added zinc dust (4.30 equiv) and calcium chloride dihydrate (2.15 equiv) at room temperature, whereupon the mixture was then heated to reflux. Color change of the solution from yellow to colorless indicated that the reaction was complete, with a reaction time of approximately 4-5 hours. The reaction mixture was filtered hot through a pad of celite and washed with hot EtOAc (100 mL). The solvent was removed under reduced pressure and partitioned with water (150 mL) and EtOAc (150 mL). The aqueous layer was then adjusted to a pH of 3-4 with 20% HCl, extracted with EtOAc (3 X 100 mL), washed with brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography (silica gel, 20:1, CH_2Cl_2:MeOH) gave the desired product.

7-Amino-3,4-dihydro-4-(*p*-methoxybenzyl)-2*H*-1,4-benzoxazine (Structure **5** of **Scheme I**, where R^6 = H, R^X = 4-anisyl). This compound was prepared by General Method 10 from 3,4-dihydro-4-(*p*-methoxybenzyl)-7-nitro-2*H*-1,4-benzoxazine (1.0 g, 3.3 mmol) and purified by flash chromatography (CH_2Cl_2/MeOH, 20:1) to afford 900 mg (99%) of 7-amino-3,4-dihydro-4-(*p*-methoxybenzyl)-2*H*-1,4-benzoxazine. Data for 7-amino-3,4-dihydro-4-(*p*-methoxybenzyl)-2*H*-1,4-benzoxazine: R_f 0.60 (24:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (d, 2H, *J* = 8.6), 6.86 (d, 2H, *J* = 8.6), 6.60 (d, 1H, *J* = 8.4), 6.34 (d, 1H, *J* = 2.5), 6.30 (dd, 1H, *J* = 8.5, 2.4), 4.25 (s, 2H), 4.21 (t, 2H, *J* = 4.5), 3.80 (s, 3H), 3.17 (t, 2H, *J* = 4.3).

(±)-1,2,3,6-Tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **120**, Structure **10** of **Scheme II**, where R^1 = H, R^2 = trifluoromethyl). This compound was prepared by General Method 5 (EXAMPLE 1) from 7-amino-3,4-dihydro-4-(*p*-methoxybenzyl)-2*H*-1,4-benzoxazine (1.78 g, 6.58 mmol) and ethyl 4,4,4,-trifluoroacetoacetate (1.15 mL, 7.9 mmol), and purified by flash chromatography (19:1 CH_2Cl_2:MeOH) to afford 533 mg (30%) of Compound **120**. Data Compound **120**: R_f

0.17 (3:2 EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.73 (br s, 1H), 6.94 (s, 1H), 6.87 (s, 1H), 6.75 (s, 1H), 4.35 (t, 2H, *J* = 4.4), 3.99 (br s, 1H), 3.50-3.42 (m, 1H).

EXAMPLE 20

1-Cyclopropylmethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **121**, Structure **11** of **Scheme II**, where R^1 = H, R^2 = trifluoromethyl , R^X = cyclopropyl).

This compound was prepared by General Method 3 (EXAMPLE 1) from Compound **120** (EXAMPLE 19) (55 mg, 0.21 mmol), cyclopropanecarboxaldehyde (100 mg, 1.5 mmol) and $NaBH_3CN$ (65 mg, 1.01 mmol) to afford 64 mg (98%) of Compound **121**. Data for Compound **121**: R_f 0.29 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.04 (br s, 1H), 7.00 (s, 1H), 6.88 (s, 1H), 6.78 (s, 1H), 4.36 (t, 2H, *J* = 4.4), 3.46 (t, 2H), *J* = 4.4), 3.19 (d, 2H, *J* = 6.3), 1.05 (m, 1H), 0.62-0.58 (m, 2H), 0.27 (m, 2H).

EXAMPLE 21

1,2,3,6-Tetrahydro-1-(2-pyridylmethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **122**, Structure **11** of **Scheme II**, where R^1 = H, R^2 = trifluoromethyl , R^X = 2-pyridyl). This compound was prepared by General Method 3 (EXAMPLE 1) Compound **120** (EXAMPLE 19) (19 mg, 0.07 mmol), 2-pyridinecarboxaldehyde (75.6 mg, 0.7 mmol) and $NaBH_3CN$ (22 mg, 0.3 mmol) to afford 9 mg (36%) of Compound **122**. Data for Compound **122**: R_f 0.17 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.48 (br s ,1H), 8.61 (d, 1H, *J* = 5.5), 7.64 (t, 1H, *J* = 6.9), 7.29 (d, 1H, *J* = 7.8), 7.19 (dd, 1H, *J* = 7.2, 5.5), 6.84 (s, 1H), 6.82 (s, 2H), 4.60 (s, 2H), 4.42 (t, 2H, *J* = 4.4), 3.60 (t, 2H, *J* = 4.5).

EXAMPLE 22

(±)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **123**, Structure **18** of **Scheme III**, where $R^2 = CF_3$, R^x = trifluoromethyl, R^1, R^6, R^7 = H).

(2-Methoxy-4-nitrophenyl)-2,2,2-(trifluoroethyl)amine. This compound was prepared according to General Method 7 (EXAMPLE 5) from 2-amino-5-nitroanisole (5.38 g, 32.0 mmol), trifluoroacetaldehyde hydrate (26.5 mL, 37.1 g, 0.320 mol), $NaBH_3CN$ (10.0 g, 0.160 mol) in 107 mL trifluoroacetic acid to afford 7.6 g (95%) of (2-methoxy-4-nitrophenyl)-2,2,2-(trifluoroethyl)amine, a light brown crystalline solid, after recrystallization (1:1 EtOAc:hexanes, 30 mL). Data for (2-methoxy-4-nitrophenyl)-2,2,2-(trifluoroethyl)amine: R_f 0.52 (2:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.87 (dd, 1H, *J* = 8.9, 2.4), 7.69 (d, 1H, *J* = 2.4), 6.96 (d, 1H, *J* = 8.9), 6.38 (broad s, 1H), 4.20 (qd, 2H, *J* = 9.3, 7.1), 4.00 (s, 3H).

(4-Amino-2-methoxyphenyl)-2,2,2-(trifluoroethyl)amine (Structure **13** of **Scheme III**, where $R^x = CF_3$). This compound was prepared according to General Method 10 (EXAMPLE 19) from (2-methoxy-4-nitrophenyl)-2,2,2-(trifluoroethyl)amine (8.40 g, 33.6 mmol), zinc dust (9.66 g, 0.148 mmol), and calcium chloride dihydrate (10.9 g, 73.9 mmol) in 300 mL 95% EtOH/water to afford to 6.7 g (90%) of (4-amino-2-methoxyphenyl)-2,2,2-(trifluoroethyl)amine, a deep purple oil. Data for (4-amino-2-methoxyphenyl)-2,2,2-(trifluoroethyl)amine: R_f 0.25 (1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.54 (d, 1H, *J* = 8.1), 6.20-6.30 (m, 2H), 4.15 (broad s, 1H), 3.81 (s, 3H), 3.68 (qd, 2H, *J* = 9.0, 7.4), 3.38 (broad s, 2H).

7-Methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-trifluoromethyl-1*H*-quinolin-2-one (Structure **14** of **Scheme III**, where R^1 = H, R^2 = trifluoromethyl, R^x = trifluoromethyl).

General Method 11: Condensation of an aniline with an acetoacetate derivative in benzene or toluene followed by a Knorr reaction in sulfuric acid. A solution of an aniline (1.0 equiv) in benzene or toluene (10 mL/mmol) and an acetoacetate derivative (1.2

equiv) was heated at reflux for 12-16 hrs. The resulting mixture was cooled to room temperature and concentrated under reduced pressure. The crude reaction mixture was diluted in concentrated sulfuric acid (8 mL/mmol) and heated to 100 °C for 6-16 hrs. The resulting mixture was poured over ice and neutralized with 6M NaOH solution to pH 7.0, extracted with CH_2Cl_2 (3 X 30 mL/mmol), washed with pH 7 phosphate buffer (50 mL/mmol) and brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated under reduced pressure. Purification was performed either by flash chromatography (silica gel, 20:1, CH_2Cl_2/MeOH) or by another specified method to afford the desired quinolone as a fluorescent-yellow solid.

7-Methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-trifluoromethyl-1*H*-quinolin-2-one (Structure **14** of **Scheme III**, where R^1 = H, R^2 = trifluoromethyl , R^X = trifluoromethyl).

This compound was prepared according to General Method 11 from (5.72 g, 26.0 mmol) and ethyl 4,4,4-trifluoroacetoacetate (4.56 mL, 5.74 g, 31.2 mmol) in 87 mL toluene, followed by treatment with 65 mL concentrated H_2SO_4 to afford 2.72 g (30.7%) of 7-methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-trifluoromethyl-1*H*-quinolin-2-one, a fluffy yellow solid, after rinsing the crude material with a 1:1 mixture of EtOAc:hexanes (60 mL). Data for 7-methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-trifluoromethyl-1*H*-quinolin-2-one: R_f 0.19 (4:1 EtOAc:CH_2Cl_2); **^{1}H NMR** (400 MHz, acetone-d_6) δ 10.87 (broad s, 1H), 7.04 (s, 1H), 6.99 (broad s, 1H), 6.73 (s, 1H), 5.54 (broad m, 1H), 4.07 (app quint, 2H, J = 8.4), 3.98 (s, 3H).

General Method 12: Transformation of a pyridone to an isopropyl imino ether with isopropyl iodide and cesium fluoride. To a suspension of pyridone (1 equiv) and CsF (4 equiv) in DMF (0.25 M) was added 2-iodopropane (4 equiv). The suspension was stirred for 18h, whereupon it was poured into cold water (25 mL/mmol) and extracted with EtOAc (2 x 25 mL/mmol). The organic layers were washed sequentially with water (2 x 15 mL/mmol) and brine (15 mL/mmol), dried over $MgSO_4$, filtered, and concentrated to afford a yellow brown solid, which was used without further purification.

2-Isopropyloxy-7-methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline: This compound was prepared by General Method 12 from 7-methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-trifluoromethyl-1*H*-quinolin-2-one (2.42 g, 7.11 mmol), CsF (4.32 g, 28.5 mmol), and 2-iodopropane (2.84 mL, 4.84 g, 28.5 mmol) in 28 mL DMF to afford 2.47 g (90.6%) of 2-isopropyloxy-7-methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline, a yellow brown solid, which was used without further purification. Data for 2-isopropyloxy-7-methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline: R_f 0.24 (9:1 hexanes:EtOAc); ^{1}**H** NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.02 (s, 1H), 7.01 (broad s, 1H), 5.48 (heptet, 1H, J = 6.3), 4.87 (broad t, 1H, J = 6.7), 4.02 (s, 3H), 3.88 (app quint, 2H, J = 8.8), 1.39 (d, 6H, J = 6.3).

7-Hydroxy-2-isopropyloxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline (Structure **15 of Scheme III**, where R^1 = H, R^2 = trifluoromethyl, R^X = trifluoromethyl): To a suspension of sodium hydride (60% mineral oil dispersion, 1.72 g, 6.13 mmol) in 20.6 mL DMF was added thiophenol (4.53 mL, 4.86 g, 44.1 mmol) at 0 °C. After the bubbling subsided, a solution of isopropyloxy-7-methoxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline (2.34 g, 6.13 mmol) in 10 mL DMF was added and the mixture was heated to 110 °C. After 5 h, the mixture was poured into cold water and neutralized with 21 mL 2 M $NaHSO_4$, and the aqueous layer was extracted with ethyl acetate (2 x 200 mL). The organic layers were washed sequentially with water (2 x 100 mL) and brine (100 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (hexanes:EtOAc, 2:1) afforded 1.71 g (75.8%) of 2-isopropyloxy-7-hydroxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline, a yellow solid. Data for 7-hydroxy-2-isopropyloxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline: R_f 0.21 (4:1 hexanes:EtOAc); ^{1}**H** NMR (400 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.05 (broad s, 1H), 7.01 (s, 1H), 6.0 (v broad s, 1H), 5.42 (hept, 1H, J = 6.1), 4.69 (broad t, 1H, J = 6.9), 3.88 (m, 2H), 1.37 (d, 6H, J = 6.1).

General Method 13: Cyclization of an α-bromoester onto an *o*-aminophenol to form a compound of Structure **16**. To a suspension of an aminophenol of Structure **15** (1 equiv) and K_2CO_3 (2.05 equiv) in DMF (0.25 M) was added the α-bromoester (1.05 equiv). The mixture was heated to 80 °C for 1h, then heated to 110 °C for 4h, then the reaction was partitioned between EtOAc (50 mL/mmol), water (25 mL/mmol) and sat'd NH_4Cl (25 mL/mmol). The aqueous layer was extracted with EtOAc (25 mL/mmol), and the combined organic layers were washed sequentially with water (2 x 25 mL/mmol), brine (25 mL/mmol), dried over $MgSO_4$, filtered and concentrated. This material was used without purification, or was purified as indicated.

7-Isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (Structure **16** of Scheme III, where $R^2 = CF_3$, $R^x =$ trifluoromethyl, R^1, R^6, $R^7 = H$): This compound was prepared by General Method 13 from 2-isopropyloxy-7-hydroxy-6-[(2,2,2-trifluoroethyl)amino]-4-(trifluoromethyl)quinoline (1.51 g, 4.10 mmol), K_2CO_3 (1.16 g, 8.40 mmol) and ethyl bromoacetate (0.719 g, 4.30 mmol) in 16.4 mL DMF to afford 1.57 g (94%) of 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one, a light yellow-brown solid, R_f 0.50 (4:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (broad s, 1H), 7.48 (s, 1H), 7.11 (s, 1H), 5.53 (hept, 1H, J = 6.2), 4.79 (s, 2H), 4.71 (q, 2H, J = 8.4), 1.41 (d, 6H).

General Method 14: Methenylation of a tertiary amide of Structure **16** and subsequent reduction with $NaBH_3CN$. To a solution of a substituted 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one derivative (1 equiv) in THF (0.15 M) was added Tebbe reagent (0.5 M in toluene, 1.1 equiv) at 0 °C. After 1h, ether (50 mL/mmol) and methanol (0.7 mL/mmol) were added sequentially, and the brown solution was allowed to warm to rt. After 30 min, the mixture was filtered through Celite, rinsed with ether, and concentrated to a deep orange-brown solid. The solid was passed quickly through a plug of silica gel or basic alumina to afford an orange solid which was carried on directly. To a suspension of the above

solid and $NaBH_3CN$ (5 equiv) in dichloroethane (0.2 M) was added acetic acid (2.5 mL/mmol) dropwise at 0 °C. The mixture bubbled vigorously, and was allowed to warm to rt. After 1 d the orange solution was poured into $NaHCO_3$ (40 mL/mmol) and extracted with EtOAc (2 x 40 mL/mmol). The organic layers were washed with brine (30 mL/mmol), dried over $MgSO_4$, filtered, and concentrated. The material was purified as indicated.

(±)-2,3-Dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **17** of **Scheme III**, where $R^2 = CF_3$, R^x = trifluoromethyl, R^1, R^6, R^7 = H). This compound was made from General Method 14 from 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (0.689 g, 1.69 mmol), Tebbe's reagent (3.7 mL, 1.9 mmol) in 11 mL THF to afford 0.728 g of (±)-2,3-dihydro-7-isopropoxy-2-methylene-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, an orange solid after filtration through silica gel. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (broad s, 1H), 7.49 (s, 1H), 7.29 (s, 1H), 5.59 (hept, 1H, *J* = 6.2), 4.95 (s, 2H), 4.91 (q, 2H, *J* = 9.1), 1.58 (d, 6H, *J* = 6.2). Subsequent treatment of the above solid (0.728 g) as described in General Method 14 with $NaBH_3CN$ (0.531 g, 8.45 mmol) and 4.2 mL acetic acid in 8.4 mL dichloroethane afforded 0.366 g (53%) of (±)-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a yellow solid, after flash chromatography (hexanes:EtOAc, 9:1). R_f 0.28 (9:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.12 (s, 1H), 7.00 (s, 1H), 5.48 (hept, 1H, *J* = 6.2), 4.26 (dd, *ABX*, 1H, *J* = 10.7, 2.4), 4.16 (dd, *ABX*, 1H, *J* = 10.7, 2.8), 3.97-4.07 (m, 1H), 3.77-3.87 (m, 1H), 3.61-3.68 (m, 1H), 1.38 (d, 6H, *J* = 6.2).

General Method 15: Hydrolysis of an isopropyl imino ether to a pyridone. A solution of the imino ether in a 3:1 acetic acid:concentrated HCl (0.1-0.2 M) solution was heated at 60-110 °C for 4-16 h. The solution was poured into sat'd $NaHCO_3$ (80 mL/mmol), extracted with EtOAc (2 x 80 mL/mmol), washed with brine (60 mL/mmol), dried over $MgSO_4$, filtered, concentrated, and purified as indicated.

(±)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **123**, Structure **18** of **Scheme III**, where R^1, R^6, R^7 = H, R^2 = CF_3, R^X = trifluoromethyl). This compound was prepared according to General Method 15 from (±)-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-g]quinoline (0.362 g, 0.887 mmol) in 1.6 mL conc. HCl and 4.8 mL acetic acid heated to 110 °C for 5h. The product was isolated by purification by flash chromatography (92:8 CH_2Cl_2:MeOH), followed by recrystallization from methanol to afford 0.164 g (50%) of Compound **123**, a yellow solid. Data for Compound **123**: HPLC (ODS, 7:3 MeOH:water, 3.0 mL/min) t_R 13.56 min; **^{1}H NMR** (400 MHz, $CDCl_3$) 11.07 (broad s, 1H), 7.08 (broad s, 1H), 6.96 (s, 1H), 6.75 (s, 1H), 4.25-4.30 (m, 2H), 4.05-4.25 (m, 2H), 3.72-3.82 (m, 1H), 1.28 (d, 3H, J = 6.6); ^{13}C (100 MHz, DMSO-d_6) 160.0, 147.7, 135.6 (q, J = 30.4), 134.3 (m), 129.9, 125.8 (q, J = 282), 122.7 (q, J = 275), 118.4 (broad s), 108.1, 106.0, 102.8, 68.8, 51.7, 50.9 (q, J = 32.2), 15.0.

EXAMPLE 23

(+)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **124**, Structure **(+)-18** of **Scheme III**, where R^1, R^6, R^7 = H, R^2 = CF_3, R^x = trifluoromethyl), and (-)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **125**, Structure **(-)-18** of **Scheme III**, where R^1, R^6, R^7 = H, R^2 = CF_3, R^x = trifluoromethyl). This compound was prepared according to General Method 9 (EXAMPLE 15) from Compound **123** (EXAMPLE 22) (10 mg, 0.03 mmol) on a semiprep Chiralpak AD column (20 x 250 mm) eluted hexanes/isopropanol (93:7), to afford 3.3 mg of Compound **124**, a yellow solid, and 3.0 mg of Compound **125**, a yellow solid. Data for Compound **124**: HPLC (Chiralpak AD, 93:7 hexanes:isopropanol, 5.0 mL/min) t_R 35.4 min; $[\alpha]_D$ = +39.3.

Data for Compound **125**: HPLC (Chiralpak AD, 93:7 hexanes:isopropanol, 5.0 mL/min) t_R 40.9 min; $[\alpha]_D$ = -41.3.

EXAMPLE 24

(±)-*trans*-1,2,3,6-Tetrahydro-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **126**, Structure **18** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Me, R^x = trifluoromethyl).

7-Isopropoxy-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (Structure **16** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Me, R^x = trifluoromethyl). This compound was prepared according to General Method 13 (EXAMPLE 22) from 2-isopropyloxy-7-hydroxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline (EXAMPLE 22) (55 mg, 0.15 mmol), ethyl 2-bromopropionate (29 mg, 0.16 mmol) and K_2CO_3 (46 mg, 0.33 mmol) in 1.5 mL DMF to afford 61 mg (96%) of 7-isopropoxy-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one. Data for 7-isopropoxy-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-

2(3*H*)-one: R_f 0.31 (9:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (broad s, 1H), 7.48 (s, 1H), 7.11 (s, 1H), 5.53 (hept, 1H, *J* = 6.2), 4.81 (q, 2H, *J* = 6.8), 4.60-4.76 (m, 2H), 1.64 (d, 3H, *J* = 6.8), 1.41 (d, 6H, *J* = 6.2).

(±)-*trans*-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **17** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Me, R^x = trifluoromethyl) and (±)-*cis*-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **17** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = Me, R^7 = H, R^x = trifluoromethyl). This compound was prepared according to General Method 14 (EXAMPLE 22) from 7-isopropoxy-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (19 mg, 0.046 mmol), Tebbe reagent (0.10 mL, 0.050 mmol) in 0.5 mL THF followed by reduction with $NaBH_3CN$ (17 mg, 0.27 mmol) in 0.23 mL HOAc and 0.46 mL dichloroethane to afford 15 mg (78%) of a 3:1 mixture of diastereomers after flash chromatography (4:1 hexanes:EtOAc). The diastereomers were separated on a Beckman HPLC (ODS Ultrasphere semi-prep column, 5 μm, 10 x 250 mm, 3.0 mL/min, 80% MeOH/water) to afford 3.5 mg (18%) of (±)-*trans*-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a yellow solid, and 6.5 mg (34%) of (±)-*cis*-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline. Data for (±)-*trans*-(±)-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: HPLC (ODS, 10 x 250 mm, 80% MeOH/water, 3 mL/min) t_R 50 min; R_f 0.54 (4:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.09 (broad s, 1H), 6.98 (s, 1H), 5.48 (hept, 1H, *J* = 6.2), 4.40 (qd, 1H, *J* = 6.5, 2.2), 3.96-4.09 (m, 1H), 3.72-3.85 (m, 1H), 3.42 (qd, *J* = 6.5, 2.0, 1H), 1.35-1.42 (m, 9H), 1.14 (d, 3H, *J* = 6.5).

Data for (±)-*cis*-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: HPLC (ODS, 10 x 250 mm, 80% MeOH/water, 3 mL/min) t_R 57 min; R_f 0.51 (4:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz,

$CDCl_3$) δ 7.27 (s, 1H), 7.09 (broad s, 1H), 6.99 (s, 1H), 5.48 (hept, 1H, J = 6.2), 4.33 (qd, 1H, J = 6.5, 1.8), 4.03-4.16 (m, 1H), 3.72-3.84 (m, 1H), 3.36 (qd, J = 6.7, 1.5), 1.38 (d, 6H, J = 6.2), 1.36 (d, 3H, J = 6.5), 1.27 (d, 3H, J = 6.6).

(±)-*trans*-1,2,3,6-Tetrahydro-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **126**, Structure **18** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Me, R^x = trifluoromethyl). This compound was prepared according to General Method 15 (EXAMPLE 22) from (±)-*trans*-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (3.5 mg, 0.0083 mmol) in 0.2 mL conc. HCl and 0.5 mL acetic acid heated to 110 °C for 3h, affording 2.5 mg (78%) of Compound **126** after flash chromatography (92:8 CH_2Cl_2:MeOH). Data for Compound **126**: R_f 0.20 (92:8 CH_2Cl_2:MeOH): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.50 (broad s, 1H), 7.01 (broad s, 1H), 6.90 (s, 1H), 6.87 (s, 1H), 4.32 (qd, 1H, J = 6.3, 1.9), 3.93-4.08 (m, 1H), 3.67-3.82 (m, 1H), 3.32 (qd, 1H, J = 6.5, 1.3), 1.34 (d, 3H, J = 6.4), 1.23 (d, 3H, J = 6.5).

EXAMPLE 25

(±)-*cis*-1,2,3,6-Tetrahydro-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **127**, Structure **18** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = Me, R^7 = H, R^x = trifluoromethyl).

This compound was prepared according to General Method 15 (EXAMPLE 22) from (±)-*cis*-2,3-dihydro-7-isopropoxy-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (EXAMPLE 24) (6.0 mg, 0.014 mmol) in 0.2 mL conc. HCl and 0.5 mL acetic acid heated to 110 °C for 3h, affording 4.5 mg (85%) of Compound **127** after flash chromatography (92:8 CH_2Cl_2:MeOH). Data for Compound **127**: R_f 0.20 (92:8 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.06 (broad s, 1H), 7.02 (broad s, 1H), 6.92 (s, 1H), 6.90 (s, 1H), 4.37 (qd, 1H, J = 6.4, 1.8), 3.83-3.98 (m, 1H), 3.68-3.82 (m, 1H), 3.38 (qd, 1H, J = 6.7, 1.6), 1.37 (d, 3H, J = 6.4), 1.11 (d, 3H, J = 6.6).

EXAMPLE 26

(±)-*trans*-3-Ethyl-1,2,3,6-tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **128**, Structure **18** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Et, R^x = trifluoromethyl).

(±)-3-Ethyl-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (Structure **16** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Et, R^x = trifluoromethyl). This compound was prepared according to General Method 13 (EXAMPLE 22) from 2-isopropyloxy-7-hydroxy-6-[2,2,2-(trifluoroethyl)amino]-4-(trifluoromethyl)quinoline (EXAMPLE 22) (70 mg, 0.19 mmol), ethyl 2-bromobutanoate (41 mg, 0.21 mmol) and K_2CO_3 (58 mg, 0.42 mmol) in 1.9 mL DMF to afford 63 mg (76%) of (±)-3-ethyl-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one. Data for (±)-3-ethyl-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one: R_f 0.47 (5.7:1 hexanes:EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) 7 .54 (broad s, 1H), 7.49 (s, 1H), 7.11 (s, 1 H), 5.53 (hept, 1H, *J* = 6.2), 4.72-4.83 (m, 1 H), 4.66 (dd, 1H, *J* = 8.5, 4.8), 4.55-4.65 (m, 1 H), 1.85-2.10 (m, 2 H), 1.41 (d, 6H, *J* = 6.2), 1.11 (t, 3H, *J* = 7.4).

(±)-*trans*-3-Ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **17** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Et, R^x = trifluoromethyl) and (±)-*cis*-3-ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **17** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = Et, R^7 = H, R^x = trifluoromethyl). This compound was prepared according to General Method 14 (EXAMPLE 22) from 3-ethyl-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (39 mg, 0.089 mmol), Tebbe reagent (0.20 mL, 0.098 mmol) in 0.9 mL THF followed by reduction with $NaBH_3CN$ (34 mg, 0.53 mmol) in 0.45 mL HOAc and 0.90 mL dichloroethane to afford 9 mg (23%) of (±)-*cis*-3-ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a yellow solid, and 7

mg of a 1:1 mixture of diastereomers after flash chromatography (9:1 hexanes:EtOAc). The diastereomers were separated on a Beckman HPLC (ODS Ultrasphere semi-prep column, 5 μm, 10 x 250 mm, 3.0 mL/min, 90% MeOH/water) to afford 3 mg (8%) of (±)-*trans*-3-ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a yellow solid.

Data for (±)-*trans*-3-ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: HPLC (ODS, 10 x 250 mm, 90% MeOH/water, 3 mL/min) t_R 16.2 min; R_f 0.25 (9:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, benzene-d_6) δ 7.70 (s, 1H), 7.28 (broad s, 1H), 7.02 (s, 1H), 5.55 (hept, 1H, J = 6.2), 3.41-3.52 (m, 2H), 2.90-3.01 (m, 1H), 2.63 (broad q, 1H, J = 6.3), 1.48-1.57 (m, 1H), 1.30 (d, 3H, J = 6.5), 1.28 (d, 3H, J = 6.5), 1.11-1.20 (m, 1H), 0.78 (t, 3H, J = 7.5), 0.76 (d, 3H, J = 6.5).

Data for (±)-*cis*-3-ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: HPLC (ODS, 10 x 250 mm, 90% MeOH/water, 3 mL/min) t_R 19.4 min; R_f 0.28 (9:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.09 (s, 1H), 6.98 (s, 1H), 5.47 (hept, 1H, J = 6.2), 4.09 (ddd, 1H, J = 7.9, 5.5, 2.0), 3.96-4.06 (m, 1H), 3.74-3.84 (m, 1H), 3.47 (qd, 1H, J = 6.5, 2.0), 1.65-1.88 (m, 1H), 1.50-1.62 (m, 1H), 1.37 (d, 6H, J = 6.2), 1.12 (d, 3H, J = 6.6), 1.10 (t, 3H, J = 7.4).

(±)-*trans*-3-Ethyl-1,2,3,6-tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **128**, Structure **18** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = H, R^7 = Et, R^X = trifluoromethyl).

This compound was prepared according to General Method 15 from (±)-*trans*-3-ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (3 mg, 0.007 mmol) in 0.1 mL conc. HCl and 1.5 mL acetic acid heated at 100 °C for 18h to afford 1.7 mg (63%) of Compound **128**, a yellow solid.

Data for Compound **128**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.83 (broad s, 1H), 6.99 (broad s, 1H), 6.91 (s, 2H), 3.92-4.05 (m, 2H), 3.68-3.79 (m, 1H), 3.41 (qd, 1H, J = 6.7, 1.4), 1.66-1.75 (m, 1H), 1.53-1.62 (m, 1H), 1.24 (d, 3H, J = 6.6), 1.01 (t, 3H, J = 7.5).

EXAMPLE 27

(±)-*cis*-3-Ethyl-1,2,3,6-tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **129**, Structure **18** of **Scheme III**, where R^1 = H, R^2 = CF_3, R^6 = Et, R^7 = H, R^x = trifluoromethyl).

This compound was prepared according to General Method 15 (EXAMPLE 22) from (±)-*cis*-3-ethyl-2,3-dihydro-7-isopropoxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (EXAMPLE 26) (8 mg, 0.018 mmol) in 0.1 mL conc. HCl and 1.5 mL acetic acid heated at 100 °C for 18h to afford 5 mg (71%) of Compound **129**, a yellow solid. Data for Compound **129**: R_f 0.19 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.48 (broad s, 1H), 7.02 (broad s, 1H), 6.97 (s, 1H), 6.93 (s, 1H), 4.04-4.10 (m, 1H), 3.86-3.97 (m, 1H), 3.69-3.80 (m, 1H), 3.42 (dq, 1H, *J* = 6.5, 1.9), 1.73-1.83 (m, 1H), 1.50-1.60 (m, 1H), 1.07-1.11 (m, 6H).

EXAMPLE 28

(±)-1,2,3,6-Tetrahydro-2-(hydroxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **130**, Structure **20** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl).

(±)-2,3-Dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **19 of Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl): To a solution of 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (EXAMPLE 22) (0.183 g, 0.448 mmol) in 4.8 mL THF was added Tebbe reagent (0.99 mL, 0.49 mmol) at 0 °C. After 1h, ether (22 mL) and MeOH (0.32 mL) were added sequentially and the mixture was allowed to warm to rt. The slurry was filtered through Celite and concentrated, and the resultant residues was filtered through a short plug of basic alumina (4:1 hexanes:EtOAc) to afford 0.20 g of (±)-2,3-dihydro-7-isopropoxy-2-methylene-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline. This residue was dissolved in 2.2 mL THF, and BH_3·THF solution (1M, 0.49 mL, 0.49 mmol) was added dropwise at 0 °C. After 15 min, the mixture was allowed to warm to rt,

whereupon 0.1 mL MeOH was added and the solution allowed to stir for 16h. The solvent was removed *in vacuo*, and the residue was redissolved in 2.2 mL THF and 0.45 mL MeOH, whereupon 0.10 mL 6N NaOH and a 35% H_2O_2 solution (0.055 mL, 60.9 mg, 0.63 mmol) was added. A precipitate was formed which was filtered with 20 mL THF. The filtrate was concentrated, and the resultant solid was dissolved in 1 mL MeOH, acidified with 0.05 mL conc. HCl, and the solution concentrated *in vacuo*. The residue was treated with 0.1 mL 6N NaOH, and partitioned between water (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2:1 hexanes:EtOAc) afforded 91 mg (48%) of (±)-2,3-dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a light amber oil. Data for (±)-2,3-dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: R_f 0.34 (2:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.17 (broad s, 1H), 7.01 (s, 1H), 5.48 (hept, 1H, *J* = 6.2), 4.50 (dd, 1H, *J* = 11.1, 1.6), 4.12-4.25 (m, 1H), 3.96-4.09 (m, 1H), 3.78-3.90 (m, 2H), 3.61-3.67 (m, 1H), 1.71 (t, 1H, *J* = 5.1), 1.38 (d, 6H, *J* = 6.2).

(±)-1,2,3,6-Tetrahydro-2-(hydroxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **130**, Structure **20** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl). A solution of (±)-2,3-dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (20 mg, 0.047 mmol) in 1.0 mL conc. HCl was heated at 90 °C for 4h, whereupon the solution was poured into cold sat'd $NaHCO_3$ (20 mL) and extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (2:1 hexanes:EtOAc) afforded 12 mg (67%) of Compound **130**, a yellow solid. Data for Compound **130**: R_f 0.21 (3:2 EtOAc: CH_2Cl_2); **^{1}H NMR** (400 MHz, acetone-d_6) δ 10.95

(broad s, 1H), 7.10 (broad s, 1H), 6.95 (s, 1H), 6.74 (s, 1H), 4.58 (dd, 1H, J = 10.9, 1.5), 4.20-4.42 (m, 3H), 4.17 (dd, 1H, J = 10.9, 2.2), 3.72-3.81 (m, 1H), 3.59-3.73 (m, 2H).

EXAMPLE 29

(±)-1,2,3,6-Tetrahydro-2-(acetoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **131**, Structure **21** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl). This compound was prepared by General Method 15 (EXAMPLE 22) from (±)-2,3-dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (EXAMPLE 28) (4.6 mg, 0.011 mmol) in 0.1 mL conc. HCl and 0.5 mL HOAc heated at 100 °C for 3h to afford 1.6 mg (35%) of Compound **131**, a yellow solid. Data for Compound **131**: R_f 0.21 (3:2 EtOAc:CH_2Cl_2); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 11.25 (broad s, 1H), 7.10 (broad s, 1H), 6.93 (s, 1H), 6.89 (s, 1H), 4.44 (dd, 1H, J = 11.0, 1.3), 4.26 (dd, 1H, *ABX*, J = 11.3, 6.0), 4.15 (dd, 1H, J = 11.0, 2.5), 4.10 (dd, *ABX*, J = 11.4, 7.9), 4.02-4.14 (m, 1H), 3.84-3.96 (m, 1H), 3.68-3.74 (m, 1H), 2.09 (s, 3H).

EXAMPLE 30

(±)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **132**, Structure **23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Me).

General Method 16: Alkylation of an alcohol of Structure **19** to compound of Structure **22** with an alkyl halide. To a solution of a compound of Structure **19** (1 equiv) and sodium hydride (60% mineral oil dispersion, 4 equiv) in THF (0.03-0.04 M) was added the specified alkyl halide (4 equiv). After TLC analysis show the consumption of starting material (6-18 h), the reaction mixture was quenched with 1 M phosphate buffer (500 mL/mmol), extracted with EtOAc (2 x 500 mL/mmol). The organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated, and purified as indicated.

(±)-2,3-Dihydro-7-isopropoxy-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **22** of **Scheme IV**, where

R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Me). This compound was prepared by General Method 16 from (±)-2,3-dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (EXAMPLE 28) (10 mg, 0.024 mmol), NaH (4.7 mg, 0.12 mmol) and iodomethane (17 mg, 0.12 mmol) in 0.6 mL THF to afford 8.3 mg (81%) of (±)-2,3-dihydro-7-isopropoxy-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a yellow solid, after flash chromatography (5:1 hexanes:EtOAc). Data for (±)-2,3-dihydro-7-isopropoxy-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: R_f 0.21 (3:1 hexanes: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.14 (broad s, 1H), 7.00 (s, 1H), 5.48 (hept, 1H, *J* = 6.2), 4.43 (dd, 1H, *J* = 11.0, 1.6), 4.16 (dd, *J* = 11.0, 2.6), 3.98-4.21 (m, 2 H), 3.67-3.73 (m, 1 H), 3.50-3.60 (m, 2 H), 3.37 (s, 3 H), 1.38 (d, 6H, *J* = 6.2).

(±)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **132**, Structure **23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Me). This compound was prepared according to General Method 15 (EXAMPLE 22) from (±)-2,3-dihydro-7-isopropoxy-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (8.3 mg, 0.019 mmol) in 0.1 mL conc. HCl and 0.5 mL acetic acid heated at 100 °C for 4.5 h to afford 6.0 mg (80%) of Compound **132**, a yellow solid. Data for Compound **132**: R_f 0.48 (2:1 EtOAc:CH_2Cl_2); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.09 (broad s, 1H), 7.06 (broad s, 1H), 6.94 (s, 1H), 6.92 (s, 1H), 4.43 (dd, 1H, *J* = 10.9, 1.2), 4.14 (dd, *J* = 10.9, 2.3), 3.93-4.12 (m, 2H), 3.63-3.70 (m, 1 H), 3.44-3.56 (m, 2H), 3.36 (s, 3H).

EXAMPLE 31

(+)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **133**, Structure (+)-**23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Me) and (-)-1,2,3,6-tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-

[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **134**, Structure (-)-**23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Me). This compound was prepared according to General Method 9 (EXAMPLE 15) from Compound **132** (5 mg, 0.013 mmol) on a semiprep Chiralpak AD column (20 x 250 mm), hexanes/isopropanol (95:5), to afford 1.8 mg of Compound **133**, a yellow solid, and 1.8 mg of Compound **134**, a yellow solid. Data for Compound **133**: HPLC (Chiralpak AD, 95:5 hexanes:isopropanol, 5.0 mL/min) t_R 35.7 min; $[\alpha]_D$ = +40.0.

Data for Compound **134**: HPLC (Chiralpak AD, 93:7 hexanes:isopropanol, 5.0 mL/min) t_R 40.9 min; $[\alpha]_D$ = -43.8.

EXAMPLE 32

(±)-2-(Ethoxymethyl)-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **135**, Structure **23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Et).

(±)-2-(Ethoxymethyl)-2,3-dihydro-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **22** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Et). This compound was prepared according to General Method 16 (EXAMPLE 30) from (±)-2,3-dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (EXAMPLE 28) (10 mg, 0.024 mmol), NaH (4.7 mg, 0.12 mmol) and iodoethane (17 mg, 0.12 mmol) in 1.0 mL THF to afford 9.8 mg (89%) of (±)-2-(ethoxymethyl)-2,3-dihydro-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a yellow oil, after flash chromatography (5:1 hexanes:EtOAc). Data for (±)-2-(ethoxymethyl)-2,3-dihydro-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: R_f 0.60 (5:1 hexanes: EtOAc); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.29 (s, 1H), 7.14 (broad s, 1H), 7.00 (s, 1H), 5.48 (hept, 1H, *J* = 6.2), 4.45 (dd, 1H, *J* = 10.9, 1.5), 4.16 (dd, *J* = 10.9, 2.5), 4.00-4.20 (m, 2H), 3.70 (broad t, 1H, *J* = 6.8), 3.54-3.63 (m, 2H), 3.50 (q, 2H, *J* = 6.9), 1.38 (d, 6H, *J* = 6.2), 1.20 (t, 3H, *J* = 7.0).

(±)-2-(Ethoxymethyl)-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **135**, Structure **23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = Et).

This compound was prepared according to General Method 15 (EXAMPLE 22) from 2-(ethoxymethyl)-2,3-dihydro-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (9.8 mg, 0.022 mmol) in 0.1 mL conc. HCl and 0.5 mL acetic acid heated at 100 °C for 4h to afford 6.0 mg (67%) of Compound **135**, a yellow solid. Data for Compound **135**: R_f 0.25 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.3 (broad s, 1H), 7.06 (broad s, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 4.44 (broad d, 1H, *J* = 11.0), 4.14 (dd, 1H, *J* = 10.9, 2.2), 3.95-4.10 (m, 2H), 3.67 (broad t, 1H, *J* = 6.9), 3.45-3.60 (m, 4H), 1.19 (t, 3H, *J* = 7.0).

EXAMPLE 33

(±)-1,2,3,6-Tetrahydro-2-(1-propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **136**, Structure **23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = *n*-Pr).

(±)-2,3-Dihydro-7-isopropoxy-2-(1-propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **22** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = *n*-Pr).

This compound was prepared according to General Method 16 (EXAMPLE 30) from (±)-2,3-dihydro-2-(hydroxymethyl)-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (EXAMPLE 28) (11 mg, 0.026 mmol), NaH (5.0 mg, 0.12 mmol) and 1-iodopropane (21 mg, 0.12 mmol) in 1.0 mL THF to afford 6 mg (50%) of (±)-2,3-dihydro-7-isopropoxy-2-(1-propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline, a yellow oil, after flash chromatography (5:1 hexanes:EtOAc). Data for (±)-2,3-dihydro-7-isopropoxy-2-(1-propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: R_f 0.57 (5:1 hexanes: EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.13 (broad s, 1H), 7.00 (s, 1H), 5.48 (hept, 1H, *J* = 6.2), 4.44 (dd, 1H, *J* = 10.9, 1.8),

4.17 (dd, 1H, J = 11.0, 2.5), 4.00-4.20 (m, 2H), 3.71 (broad t, 1H, J = 6.8), 3.54-3.64 (m, 2H), 3.40 (broad t, 2H, J = 6.6), 1.52-1.62 (m, 2H), 1.38 (d, 6H, J = 6.2), 0.91 (t, 3H, J = 7.4).

(±)-1,2,3,6-Tetrahydro-2-(1-propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **136**, Structure **23** of **Scheme IV**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl, R^5 = *n*-Pr). This compound was prepared according to General Method 15 (EXAMPLE 22) from (±)-2,3-dihydro-7-isopropoxy-2-(1-propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (6.0 mg, 0.013 mmol) in 0.1 mL conc. HCl and 0.5 mL acetic acid heated at 100 °C for 4h to afford 3.1 mg (56%) of Compound **136**, a yellow solid. Data for Compound **136**: R_f 0.25 (11.5:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.75 (broad s, 1H), 7.06 (broad s, 1H), 6.92 (s, 1H), 6.90 (s, 1H), 4.44 (dd, 1H, J = 10.9, 1.7), 4.14 (dd, 1H, J = 10.9, 2.5), 3.94-4.08 (m, 2H), 3.65-3.70 (m, 1H), 3.47-3.59 (m, 2H), 3.39 (t, 2H, J = 6.6), 1.50-1.62 (m, 2 H), 0.91 (t, 3H, J = 7.4).

EXAMPLE 34

1,6-Dihydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-3*H*-[1,4]oxazino[3,2-*g*]-quinolin-2,7-dione (Compound **137**, Structure **24** of **Scheme V**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl). This Compound was prepared according to General Method 15 (EXAMPLE 22) from 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (EXAMPLE 22) (72 mg, 0.18 mmol), in 0.5 mL conc. HCl and 2.0 mL acetic acid heated at 60 °C for 16 h to afford 42 mg (65%) of Compound **137**, an off-white solid, after flash chromatography (92:8 CH_2Cl_2:MeOH). Data for Compound **137**: R_f 0.34 (92:8 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, acetone-d_6) δ 11.11 (broad s, 1H), 7.52 (s, 1H), 7.18 (s, 1H), 6.86 (s, 1H), 4.95 (q, 2H, J = 9.0), 4.90 (s, 2H).

EXAMPLE 35

(±)-1,2,3,6-Tetrahydro-2-hydroxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **138**, Structure **25** of **Scheme V**, where, R^1, R^6, R^7 = H, R^4 = Me, R^2 = trifluoromethyl). To a solution of Compound **137** (EXAMPLE 34) (0.012 g, 0.033 mmol) in 1 mL THF and 0.1 mL HMPA and was added MeLi solution (1.4 M in ether, 0.12 mL, 0.16 mmol) at –78 °C for 0.5 h. The reaction was quenched with 20 mL phosphate buffer (pH = 7) and extracted with EtOAc (2 x 20 mL). The organic fractions were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (5% methanol/ CH_2Cl_2) gave 8 mg (62% yield) of Compound **138**, a yellow solid. **^{1}H NMR** (400MHz, acetone-d_6) 10.92 (br s, 1H), 7.13 (br s, 1H), 6.96 (s, 1H), 6.75 (s, 1H), 4.34-4.24 (m, 1H), 4.23 (d, 1H, *J* = 11.6), 4.19 (d, 1H, *J* = 10.8), 4.07-3.96 (m, 1H), 1.49 (s, 3H).

EXAMPLE 36

1,6-Dihydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-3*H*-[1,4]oxazino[3,2-*g*]-quinolin-2,7-dione (Compound **139**, Structure **24** of **Scheme V**, where R^1, R^6 = H, R^2 = trifluoromethyl, R^7 = Me): A mixture of 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (EXAMPLE 22) (7.0 mg, 0.017 mmol) in 0.5 mL 57% HI was heated to 65 °C for 16h, whereupon it was poured onto cold $NaHCO_3$ (25 mL). The mixture was extracted with EtOAc (25 mL), and the organic layer was washed sequentially with 1 M phosphate buffer (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (92:8 CH_2Cl_2:MeOH) afforded 1.4 mg (22%) of Compound **139**, an off-white solid. Data for Compound **139**: R_f 0.37 (92:8 CH_2Cl_2:MeOH; ^{1}**H NMR** (400 MHz, acetone-d_6) δ 11.09 (broad s, 1H), 7.52 (s, 1H), 7.19 (s, 1H), 6.86 (s, 1H), 4.80-5.05 (m, 3H), 1.59 (d, 3H, J = 6.7).

EXAMPLE 37

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-2-thioxo-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **140**, Structure **27** of **Scheme V**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl).

7-Isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-thione (Structure **26** of **Scheme V**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl). A mixture of 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-one (EXAMPLE 22) (48.4 mg, 0.119 mmol) and Lawesson's reagent (0.144 g, 0.356 mmol) in 2.4 mL toluene was heated at reflux for 6h, whereupon the mixture was partitioned between EtOAc (40 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (20 mL), and the combined organic layers were washed with brine (20 mL), dried over MgSO4, filtered, and concentrated. Flash chromatography (9:1 hexanes:EtOAc) afforded 41 mg of 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-thione, a

yellow oil. Data for 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-thione: R_f 0.36 (9:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (broad s, 1H), 7.48 (s, 1H), 7.13 (s, 1H), 5.54 (hept, 1H, J = 6.2), 5.32-5.42 (m, 2H), 5.05 (s, 2H), 1.41 (d, 6H, J = 6.2).

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-2-thioxo-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **140**, Structure **27 of Scheme V**, where R^1, R^6, R^7 = H, R^2 = trifluoromethyl). To a solution of 7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinolin-2(3*H*)-thione (30 mg, 0.071 mmol) in 1.4 mL CH_2Cl_2 was added BCl_3 (1 M in CH_2Cl_2, 1.2 mL, 1.2 mmol). After 8h, the mixture was quenched with saturated $NaHCO_3$ (15 mL) and extracted with EtOAc (2 x 15 mL). The organic layers were washed with brine (15 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (3:2 CH_2Cl_2:EtOAc) afforded 17 mg (63%) of Compound **140**, an off-white solid. Data for Compound **140**: R_f 0.36 (3:2 CH_2Cl_2:EtOAc); **^{1}H NMR** (400 MHz, acetone-d_6) δ 11.22 (broad s, 1H), 7.72 (broad s, 1H), 7.19 (s, 1H), 6.90 (s, 1H), 5.62-5.75 (m, 2H), 5.16 (s, 2H).

EXAMPLE 38

(±)-1,2,3,6-Tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **141**, Structure **30 of Scheme VI**, where R^4 = Me).

(2-Methoxy-4-nitrophenyl)-(4-methoxybenzyl)amine. This compound was prepared according to General Method 3 (EXAMPLE 1) from 2-amino-5-nitroanisole (1.00 g, 5.95 mmol), *p*-anisaldehyde (1.62 g, 11.9 mmol), $NaBH_3CN$ (0.373 g, 5.95 mmol) in 100 mL acetic acid to afford 1.25 g (75%) of (2-methoxy-4-nitrophenyl)-(4-methoxybenzyl)amine, an orange solid, after washing the crude product with 4:1 hexanes:EtOAc. Data for (2-methoxy-4-nitrophenyl)-(4-methoxybenzyl)amine: R_f 0.80 (3:2 EtOAc:hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (dd, 1H, J = 8.8, 2.4), 7.64 (d,

1H, J = 2.4), 7.22-7.28 (m, 2H), 6.85-6.90 (m, 2H), 6.51 (d, 1H, J = 9.0), 5.31 (broad s, 1H), 4.38 (d, 2H, J = 5.4), 3.93 (s, 3H), 3.82 (s, 3H).

(4-Amino-2-methoxyphenyl)-(4-methoxybenzyl)amine (Structure **13** of **Scheme III**, where R^X = 4-anisyl). This compound was prepared by General Method 10 (EXAMPLE 19) from (2-methoxy-4-nitrophenyl)-(4-methoxybenzyl)amine (1.92 g, 6.65 mmol), zinc dust (1.87 g, 28.6 mmol), and calcium chloride dihydrate (2.10 g, 14.3 mmol) in 350 mL 95:5 EtOH:water to afford 1.23 g (70%) of (4-amino-2-methoxyphenyl)-(4-methoxybenzyl)amine, a light purple solid, after flash chromatography (CH_2Cl_2:MeOH 19:1). Data for (4-amino-2-methoxyphenyl)-(4-methoxybenzyl)amine: R_f 0.80 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (d, 2H, J = 8.6), 6.87 (d, 2H, J = 8.6), 6.47 (d, 1H, J = 8.1), 6.28 (d, 1H, J = 2.4), 6.23 (dd, 1H, J = 8.1, 2.4), 4.20 (s, 2H), 4.10 (v broad s, 1H), 3.80 (s, 3H), 3.79 (s, 3H), 3.31 (broad s, 2H).

6-Amino-7-methoxy-4-(trifluoromethyl)-1*H*-quinolin-2-one. This compound was prepared according to General Method 11 (EXAMPLE 22) from (4-amino-2-methoxyphenyl)-(4-methoxybenzyl)amine (1.23 g, 4.76 mmol) and ethyl 4,4,4-trifluoroacetoacetate (1.05 g, 5.71 mmol) in 60 mL benzene followed by treatment with 10 mL concentrated H_2SO_4 to afford 0.734 (60%) of 6-amino-7-methoxy-4-(trifluoromethyl)-1*H*-quinolin-2-one, a yellow solid, after rinsing with MeOH:ether:hexanes. Data for 6-amino-7-methoxy-4-(trifluoromethyl)-1*H*-quinolin-2-one: R_f 0.28 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.2 (v broad s, 1H), 7.06 (broad s, 1H), 6.93 (s, 1H), 6.79 (s, 1H), 4.01 (s, 3H), 3.94 (broad s, 2H).

6-Amino-2-isopropoxy-7-methoxy-4-(trifluoromethyl)quinoline. This compound was prepared according to General Method 12 (EXAMPLE 22) from 6-amino-7-methoxy-4-(trifluoromethyl)-1*H*-quinolin-2-one (500 mg, 1.9 mmol), CsF (1.18 g, 7.7 mmol), isopropyl iodide (1.31 g, 7.7 mmol) in 8 mL DMF to afford 308 mg (53%) of 6-amino-2-isopropyloxy-7-methoxy-4-(trifluoromethyl)quinoline, a light yellow oil, and 190 mg (29%) of 2-isopropyloxy-7-methoxy-6*N*-(isopropyl)amino-4-(trifluoromethyl)quinoline, after flash chromatography (7:3 hexanes:EtOAc). Data for 6-

amino-2-isopropyloxy-7-methoxy-4-(trifluoromethyl)quinoline: R_f 0.51 (4:1 hexanes:EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.18 (s, 1H), 7.13 (broad s, 1H), 7.00 (s, 1H), 5.48 (hept, 1H, J = 6.3), 4.11 (broad s, 2H), 4.01 (s, 3H), 1.40 (d, 6H, J = 6.3).

6-Amino-7-hydroxy-2-isopropyloxy-4-(trifluoromethyl)quinoline (Structure **28** of **Scheme VI**). To a suspension of sodium hydride (60% mineral oil dispersion, 180 mg, 4.6 mmol, rinsed with hexanes) in 3.5 mL DMF was added thiophenol (550 mg, 5.0 mmol) at 0 °C, whereupon a solution of 6-amino-2-isopropyloxy-7-methoxy-4-(trifluoromethyl)quinoline (200 mg, 0.67 mmol) in 2 mL DMF was added. The mixture was heated at 110 °C for 6h, then poured into ice, and the pH was adjusted to 5 by the addition of 2N $NaHSO_4$. The mixture was extracted with EtOAc (2 x 30 mL), washed sequentially with water (30 mL) and brine (30 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (4:1 hexanes:EtOAc) afforded 147 mg (77%) of 6-amino-2-isopropyloxy-7-methoxy-4-(trifluoromethyl)quinoline, a tan solid. Data for 6-amino-2-isopropyloxy-7-methoxy-4-(trifluoromethyl)quinoline: R_f 0.14 (4:1 hexanes:EtOAc); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.19 (broad s, 1H), 7.16 (s, 1H), 6.99 (s, 1H), 5.60 (v. broad s, 1H), 5.45 (hept, 1H, J = 6.2), 4.00 (v. broad s, 2H), 1.38 (d, 6H, J = 6.3).

General Method 17. Alkylation of an α-halo-ketone to an *o*-aminophenol and subsequent reductive cyclization to a 1,4-oxazine derivative. To a solution of 2-amino-5-nitrophenol (1.0 equiv) in acetone (0.6 mL/mmol) was added an α-halo ketone (1.1 equiv) and K_2CO_3 (1.1 equiv) at 0 °C under N_2. The reaction mixture was allowed to warm to room temperature and stirred for 6-8 hours. The crude reaction mixture was then evaporated under reduced pressure and washed with water (3 X 100 mL) and the resulting solid was dried under high vacuum. To this crude solid (1.0 equiv) in trifluoroacetic acid (0.26 M) was added portionwise $NaBH_3CN$ (1.0 equiv) and stirred at room temperature under N_2 overnight. The resulting mixture was poured over ice and neutralized with 6M NaOH to pH 7.0, extracted with EtOAc (3 X 30 mL/mmol), washed with brine (50 mL/mmol). The organic solution was dried ($MgSO_4$) and concentrated

under reduced pressure. Purification by flash chromatography (silica gel, 19:1, CH_2Cl_2/MeOH) afforded the desired 1,4-oxazine derivative.

(±)-2,3-Dihydro-7-isopropoxy-2-methyl-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **29** of **Scheme VI**, where R^4 = Me). This compound was prepared by General Method 17 from 6-amino-3,4-dihydro-7-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (15 mg, 0.05 mmol), chloroacetone (5.0 μL, 0.06 mmol), and K_2CO_3 (8.0 mg, 0.06 mmol) to afford 13 mg of crude solid. The crude solid (13 mg, 0.04 mmol), $NaBH_3CN$ (2.5 mg, 0.04 mmol) and trifluoroacetic acid afforded 10.0 mg (77%) of (±)-2,3-dihydro-7-isopropoxy-2-methyl-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline. Data for (±)-2,3-dihydro-7-isopropoxy-2-methyl-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: R_f 0.84 (2:3, EtOAc:hexanes); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.02 (d, 1H, *J* = 2.0), 6.97 (s, 1H), 5.48 (m, 1H), 4.30 (dd, 1H, *J* = 10.6, 2.7), 4.12 (br s, 1H), 3.88 (dd, 1H, *J* = 10.7, 8.3), 3.64 (m, 1H), 1.38 (d, 6H, *J* = 6.3), 1.24 (d, 3H, *J* = 6.8).

(±)-1,2,3,6-Tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **141**, Structure **30** of **Scheme VI**, where R^4 = Me). This compound was prepared by General Method 15 (EXAMPLE 22) from (±)-2,3-dihydro-7-isopropoxy-2-methyl-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (10.0 mg, 0.03 mmol) in 0.2 mL HCl and 1 mL HOAc heated at 80 °C for 6 h to afford 7.0 mg (77%) of Compound **141**, a yellow solid, after purification by flash chromatography (3:2, EtOAc/hexanes). Data for Compound **141**: R_f 0.31 (3:2, EtOAc:hexanes); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 12.14 (br s, 1H), 6.94 (s, 1H), 6.89 (s, 2H), 4.29 (dd, 1H, *J* = 8.3, 2.0), 3.94 (br s, 1H), 3.86 (dd, 1H, *J* = 10.5, 8.5), 3.58 (m, 1H), 1.23 (d, 3H, *J* = 6.3).

EXAMPLE 39

(±)-1-Cyclopropylmethyl-1,2,3,6-tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **142**, Structure **31** of **Scheme VI**, where R^4 = Me, R^x = cyclopropyl). This compound was prepared by General Method 3

(EXAMPLE 1) from Compound **141** (7.0 mg, 0.02 mmol), cyclopropane carboxaldehyde (17.3 mg, 0.2 mmol) and $NaBH_3CN$ (7.7 mg, 0.1 mmol) to afford 6.6 mg (82%) of Compound **142**. Data for Compound **142**: R_f 0.36 (3:2, EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.58 (br s, 1H), 6.98 (s, 1H), 6.89 (s, 1H), 6.85 (s, 1H), 4.26 (dd, 1H, J = 10.7, 2.4), 4.14 (dd, 1H, J = 10.5, 2.7), 3.72 (m, 1H), 3.32 (dd, 1H, J = 14.6, 5.8), 3.02 (dd, 1H, J = 14.6, 4.3), 1.22 (d, 3H, J = 6.3), 1.05 (m, 1H), 0.63 (m, 2H), 0.3 (m, 2H).

EXAMPLE 40

(±)-2-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **143**, Structure **30** of **Scheme VI**, where R^4 = Et).

(±)-2-Ethyl-2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (Structure **29** of **Scheme VI**, where R^4 = Et). This compound was prepared by General Method 17 (EXAMPLE 38) from 6-amino-7-hydroxy-2-isopropoxy-4-(trifluoromethyl)quinoline (EXAMPLE 36) (15 mg, 0.05 mmol), 1-bromo-2-butanone (6.0 μL, 0.06 mmol), and K_2CO_3 (8.0 mg, 0.06 mmol) to afford 16 mg of crude solid. The crude solid (16 mg, 0.05 mmol), $NaBH_3CN$ (3.0 mg, 0.05 mmol) and trifluoroacetic acid afforded 13 mg (81%) of (±)-2-ethyl-2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline. Data for (±)-2-ethyl-2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline: R_f 0.78 (2:3, EtOAc:hexanes) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.22 (s, 1H), 7.01 (s, 1H), 6.96 (s, 1H), 5.47 (m, 1H), 4.33 (dd, 1H, J = 10.6, 2.5), 4.20 (br s, 1H), 3.95 (dd, 1H, J = 10.6, 7.9), 3.40 (m, 1H), 1.58 (m, 2H), 1.37 (d, 6H, J = 6.1), 1.06 (t, 3H, J = 7.5).

(±)-2-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **143**, Structure **30** of **Scheme VI**, where R^4 = Et). This compound was prepared by General Method 15 (EXAMPLE 22) from (±)-2-ethyl-2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline (13.0 mg, 0.04 mmol) and was purified by flash chromatography (3:2, EtOAc/hexanes) to yield 8.1 mg (72%) of Compound **143**. Data Compound **143**: R_f 0.34 (3:2, EtOAc:hexanes); **^{1}H**

NMR (400 MHz, $CDCl_3$) δ 12.11 (br s, 1H), 6.95 (s, 1H), 6.89 (s, 1H), 6.88 (s, 1H), 4.34 (dd, 1H, *J* = 10.2, 2.5), 4.02 (br s, 1H), 3.93 (dd, 1H, *J* = 10.7, 7.8), 3.35 (m, 1H), 1.56 (m, 2H), 1.06 (t, 3H, *J* = 7.5).

EXAMPLE 41

(±)-1-(Cyclopropylmethyl)-2-ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **144**, Structure **31** of **Scheme VI**, where R^4 = Et, R^X = cyclopropyl). This compound was prepared by General Method 3 (EXAMPLE 1) from Compound **143** (8.1 mg, 0.03 mmol), cyclopropane carboxaldehyde (19.1 mg, 0.2 mmol) and $NaBH_3CN$ (8.5 mg, 0.1 mmol) and purified by HPLC (75:25 MeOH:water, semi-prep ODS column @ 3 mL/min) to afford 4.0 mg (44%) of Compound **144**. Data for Compound **144**: R_f 0.30 (3:2, EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.72 (br s, 1H), 6.96 (s, 1H), 6.89 (s, 1H), 6.85 (s, 1H), 4.34 (dd, 1H, *J* = 10.7, 1.9), 4.15 (dd, 1H, *J* = 10.7, 2.4), 3.39 (m, 2H), 3.0 (m, 1H), 1.59 (m, 2H), 1.06 (m, 1H), 0.98 (t, 3H, *J* = 7.8), 0.62 (m, 2H), 0.29 (m, 2H).

EXAMPLE 41A

1,2,3,6-Tetrahydro-1-isopropyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **144A**, Structure **31D** of **Scheme VIA**, where R^1 = R^4 = R^6 = H, R^2 = trifluoromethyl, R^{13} = isopropyl).

2-Isopropyloxy-6-isopropylamino-7-methoxy-4-(trifluoromethyl)quinoline (Structure **31B** of **Scheme VIA**, where R^1 = H, R^2 = trifluoromethyl, R^{13} = isopropyl, R^A = isopropyloxy). A suspension of 6-amino-7-methoxy-4-trifluoromethyl-1*H*-quinolin-2-one (0.50 g, 1.9 mmol), CsF (1.18 g, 7.7 mmol) and isopropyl iodide (1.31 g (7.7 mmol) in 8 mL DMF was stirred at 30 °C for 18 h, whereupon the mixture was quenched with pH 7 phosphate buffer and extracted with EtOAc (2 x). The combined organic layers were washed sequentially with water (2 x) and brine, dried over Na_2SO_4, filtered and concentrated. Flash chromatography (7:3, hexanes:EtOAc) afforded 0.19 g (32%) of 2-isopropyloxy-6-isopropylamino-7-methoxy-4-(trifluoromethyl)quinoline, an

oil. Data for Compound 2-isopropyloxy-6-isopropylamino-7-methoxy-4-(trifluoromethyl)quinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 6.99 (s, 1H), 6.87 (s, 1H), 5.47 (sept, 1H, J = 6.2), 4.37 (d, 1H, J = 7.4), 3.99 (s, 3H), 3.70-3.80 (m, 1H), 1.39 (d, 6H, J = 6.2), 1.30 (d, 6H, J = 6.2).

2-Isopropyloxy-7-hydroxy-6-isopropylamino-4-(trifluoromethyl)quinoline (Structure **31C of Scheme VIA**, where R^1 = H, R^2 = trifluoromethyl, R^{13} = isopropyl, R^A = isopropyloxy). A solution of 2-isopropyloxy-6-isopropylamino-7-methoxy-4-(trifluoromethyl)quinoline (0.10 g, 0.30 mmol), thiophenol (0.24 g, 2.2 mmol), and NaH (60% dispersion in mineral oil, 78 mg, 2.0 mmol) in 2 mL DMF was heated at 110 °C for 5 h, whereupon the mixture was poured over ice, and adjusted to pH 5 with 2M $NaHSO_4$. The aqueous layer was extracted with EtOAc (2 x), and the combined organic layers were washed sequentially with water (2 x) and brine, dried over $MgSO_4$, filtered and concentrated. Flash chromatography (4:1 hexanes:EtOAc) afforded 90 mg (95%) of 2-isopropyloxy-7-hydroxy-6-isopropylamino-4-(trifluoromethyl)quinoline, a yellow oil. Data for 2-isopropyloxy-7-hydroxy-6-isopropylamino-4-(trifluoromethyl)quinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.16 (s, 1H), 6.98 (s, 1H), 6.92 (s, 1H), 5.37 (sept, 1H, J = 6.2), 3.70 (sept, 1H, J = 6.3), 1.35 (d, 6H, J = 6.2), 1.29 (d, 6H, J = 6.3).

1,2,3,6-Tetrahydro-1-isopropyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **144A**, Structure **31D of Scheme VIA**, where $R^1 = R^4 = R^6$ = H, R^2 = trifluoromethyl, R^{13} = isopropyl). A suspension of 2-isopropyloxy-7-hydroxy-6-isopropylamino-4-(trifluoromethyl)quinoline (60 mg, 0.18 mmol), 1,2-dibromoethane (62 mg, 0.33 mmol) and K_2CO_3 (47 mg, 0.34 mmol) in 3 mL acetone and 1.5 mL water was heated at reflux for 18 h, whereupon the mixture was partitioned between water and EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (4:1 hexanes:EtOAc) afforded 27 mg of a yellow oil which was carried on directly by treatment with 0.05 mL concentrated HCl and 0.5 mL HOAc and heated at 70 °C for 4h, whereupon the reaction was poured over ice and adjusted to pH 7 with 25% aqueous NaOH. The aqueous layer was extracted with EtOAc (3 x), and the combined

organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (3:2 hexanes:EtOAc) afforded 10 mg (30%) of Compound **144A**, a yellow solid. Data for Compound **144A**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.0 (broad s, 1H), 6.99 (s, 1H), 6.87 (s, 1H), 6.80 (s, 1H), 4.34 (t, 2H, J = 4.6, 2H), 4.08 (sept, 1H, J = 6.3), 3.26 (t, 2H, J = 4.6), 1.22 (d, 6H, J = 6.3).

EXAMPLE 42

(±)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **145**, Structure **35** of **Scheme VII**, where R^1 = H, R^2 = CF_3, R^4 = Et, R^X = trifluoromethyl).

(±)-3-Ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (Structure **32** of **Scheme VII**, where R^4 = Et). This compound was prepared by General Method 17 (EXAMPLE 38) from 2-amino-5-nitrophenol (2.0 g, 13.0 mmol), 1-bromo-2-butanone (1.45 mL, 14.2 mmol), and K_2CO_3 (1.97 g, 14.2 mmol) to afford 3.0 g of crude solid. The crude solid (3.0 g, 13.3 mmol), $NaBH_3CN$ (837 mg, 13.3 mmol) and trifluoroacetic acid afforded 1.96 g (70%) (±)-3-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine after purification by flash chromatography (19:1, CH_2Cl_2/MeOH). Data for (±)-3-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine: R_f 0.57 (2:3 EtOAc:hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 (dd, 1H, *J* = 8.7, 2.6), 7.69 (d, 1H, *J* = 2.6), 6.51 (d, 1H, *J* = 8.8), 4.59 (br s, 1H), 4.25 (dd, 1H, *J* = 10.7, 3.2), 3.86 (dd, 1H, *J* = 10.7, 7.1), 3.43 (m, 1H), 1.6 (m, 2H), 1.05 (t, 3H, *J* = 7.4).

(±)-3-Ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **33** of **Scheme VII**, where R^4 = Et, R^X = CF_3). This compound was prepared by General Method 7 (EXAMPLE 5) from (±)-3-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (200 mg, 0.96 mmol), 2,2,2-trifluoroacetaldehyde monohydrate (1.12 g, 9.6 mmol) and $NaBH_3CN$ (292 mg, 4.6 mmol) to afford 100 mg (36%) of 3-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine, a yellow solid. Data for (±)-3-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.69 (2:3

EtOAc:hexanes); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, 1H, *J* = 8.9, 2.6), 7.71 (d, 1H, *J* = 2.6), 6.72 (d, 1H, *J* = 9.0), 4.34 (dd, 1H, *J* = 10.9, 1.4), 4.19-4.05 (m, 1H), 4.02 (dd, 1H, *J* = 11.0, 2.3), 3.87-3.72 (m, 1H), 1.72-1.62 (m, 2H), 1.00 (t, 3H, *J* = 7.4).

(±)-7-Amino-3-ethyl-3,4-dihydro-4-[2,2,2(trifluoroethyl)]-2*H*-1,4-benzoxazine (Structure **34** of **Scheme VII**, where R^4 = Et, R^x = CF_3). This compound was prepared by General Method 4 (EXAMPLE 1) from (±)-3-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (100 mg, 0.34 mmol) and purified by flash chromatography (EtOAc:hexanes, 3:2) to afford 83 mg (93%) of (±)-7-amino-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine. Data for (±)-7-amino-3-ethyl-3,4-dihydro-4-[2,2,2(trifluoroethyl)]-2*H*-1,4-benzoxazine: R_f 0.63 (3:2 EtOAc:hexanes); ^{1}**H NMR** (400 MHz, $CDCl_3$) δ 6.64 (d, 1H, *J* = 8.3), 6.28 (dd, 1H, *J* = 8.5, 2.7), 6.23 (d, 1H, *J* = 2.4), 4.15 (d, 1H, *J* = 10.7), 3.96 (dd, 1H, *J* = 10.7, 2.4), 3.65 (m, 1H), 3.40 (br s, 1H), 3.03 (m, 1H), 1.53 (m, 2H), 0.96 (t, 3H, *J* = 7.6).

(±)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **145**, Structure **35** of **Scheme VII**, where R^1 = H, R^2 = CF_3, R^4 = Et, R^x = trifluoromethyl). This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-7-amino-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (83 mg, 0.32 mmol) and ethyl 4,4,4-trifluoroacetoacetate (70 mg, 0.38 mmol) and purified by flash chromatography (3:2 EtOAc:hexanes) to yield 54 mg (44%) of Compound **145**. Data for Compound **145**: R_f 0.36 (3:2 EtOAc:hexanes); ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 11.67 (br s, 1h), 7.07 (s, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 4.35 (dd, 1H, *J* = 10.7. 2.0), 4.15 (dd, 1H, *J* = 10.7, 2.4), 4.04-3.97 (m, 1H), 3.75 (m, 1H), 3.28 (m, 1H), 1.64 (m, 2H), 1.00 (t, 3H, *J* = 7.3).

EXAMPLE 43

(±)-1,2-Diethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **146**, Structure **35 of Scheme VII**, where R^1 = H, R^2 = CF_3, R^4 = Et, R^x = CH_3).

(±)-3,4-Diethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (Structure **33 of Scheme VII**, where R^4 = Et, R^x = CH_3). This compound was prepared by General Method 3 (EXAMPLE 1) from 3-ethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (EXAMPLE 42) (200 mg, 0.96 mmol), acetaldehyde (424 mg, 9.6 mmol) and $NaBH_3CN$ (293 mg, 4.6 mmol) to afford 170 mg (75%) of (±)-3,4-diethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine, a yellow solid. Data for (±)-3,4-diethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine: R_f 0.80 (3:2 EtOAc:hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, 1H, J = 8.9, 2.6), 7.66 (d, 1H, J = 2.6), 6.55 (d, 1H, J = 9.2), 4.07 (dd, *ABX*, 1H, J = 10.7, 2.5), 3.96 (dd, *ABX*, 1H, J = 10.7, 2.6), 3.60 (m, 1H), 3.55-3.35 (m, 2H), 1.29 (d, 3H, J = 6.6), 1.24 (t, 3H, J = 7.0).

(±)-7-Amino-3,4-diethyl-3,4-dihydro-2*H*-1,4-benzoxazine (Structure **34 of Scheme VII**, where R^4 = Et, R^x = CH_3). This compound was prepared by General Method 4 (EXAMPLE 1) from (±)-3,4-diethyl-3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine (170 mg, 0.72 mmol) and purified by flash chromatography (EtOAc:hexanes, 3:2) to afford 39 mg (25%) of (±)-7-amino-3,4-diethyl-3,4-dihydro-2*H*-1,4-benzoxazine. Data for (±)-7-amino-3,4-diethyl-3,4-dihydro-2*H*-1,4-benzoxazine: (3:2 EtOAc:hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.57 (d, 1H, *J* = 8.3), 6.26-6.20 (m, 2H), 4.12 (dd, *ABX*, 1H, *J* = 10.3, 2.4), 3.92 (dd, *ABX*, 1H, *J* = 10.7, 2.4), 3.32-3.28 (m, 3H), 3.15-3.10 (m, 1H), 3.01 (m, 1H), 1.57-1.48 (m, 2H), 1.15 (t, 3H, *J* = 7.0), 0.94 (t, 3H, *J* = 7.3).

(±)-1,2-Diethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **146**, Structure **35 of Scheme VII**, where R^1 = H, R^2 = CF_3, R^4 = Et, R^x = CH_3). This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-7-amino-3,4-diethyl-3,4-dihydro-2*H*-1,4-benzoxazine (39 mg, 0.18 mmol) and ethyl 4,4,4-trifluoroacetoacetate (42 mg, 0.22 mmol) and purified by flash chromatography (19:1, CH_2Cl_2/MeOH) to yield 15 mg (25%) of Compound **146**. Data

for Compound **146**: R_f 0.28 (19:1, CH_2Cl_2:MeOH); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.50 (br s, 1H), 6.89 (s, 1H), 6.88 (s, 1H), 6.84 (s, 1H), 4.32 (dd, *ABX*, 1H, *J* = 10.7, 2.0), 4.06 (dd, *ABX*, 1H, *J* = 10.7, 2.7), 3.51-3.47 (m, 1H), 3.30-3.23 (m, 2H), 1.66-1.60 (m, 2H), 1.25 (t, 3H, *J* = 7.3), 0.98 (t, 3H, *J* = 7.3).

EXAMPLE 43A

(±)-1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **146A**, Structure **35** of **Scheme VII**, where R^1 = H, R^2, R^4 = trifluoromethyl, R^x = CF_3).

2-(Trifluoroethyl)amino-5-nitrophenol (Structure **32A** of **Scheme VIIA**, where R^x = CF_3). This compound was prepared by General Method 7 (EXAMPLE 5) from 2-amino-5-nitrophenol (5.0 g, 32 mmol), 2,2,2-trifluoroacetaldehyde ethyl hemiacetal (9.4 g, 65 mmol) and $NaBH_3CN$ (4.1 g, 65 mmol) in 90 mL trifluoroacetic acid to afford 5.5 g (72%) of 2-(trifluoroethyl)amino-5-nitrophenol, a yellow solid, after flash chromatography (3:1 hexanes:EtOAc). Data for 2-(trifluoroethyl)amino-5-nitrophenol: **^{1}H NMR** (400MHz, acetone-d_6) 9.48 (broad s, 1H), 7.79 (dd, 1H, *J* = 9.1, 2.4), 7.67 (d, 1H, *J* = 2.4), 6.96 (d, 1H, *J* = 8.8), 6.20 (broad s, 1H), 4.26-4.18 (m, 2H)

(±)-3,4-Dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (Structure **33** of **Scheme VIIA**, where R^4 = trifluoromethyl, R^x = CF_3). This compound was prepared by General Method 17 (EXAMPLE 38) from 2-(trifluoroethyl)amino-5-nitrophenol (1.00 g, 4.23 mmol), 3-bromo-1,1,1-trifluoroacetone (4.84 g, 25.4 mmol), and K_2CO_3 (2.34 g, 16.9 mmol) to afford 1.5 g of crude solid. This was combined with another lot of the same reaction (4.2 mmol) and purified by flash chromatography (1:1 hexanes:EtOAc) to afford 1.0 g (40%) of a yellow oil. This material (725 mg, 2.47 mmol) was treated with 20 mL trifluoroacetic acid and $NaBH_3CN$ (776 mg, 12.4 mmol) to afford 0.26 g (38%) (±)-3,4-dihydro-7-nitro-3-(trifluoromethyl)-2*H*-1,4-benzoxazine after purification by flash chromatography (3:1 hexanes:EtOAc). Data for (±)-3,4-dihydro-7-nitro-3-(trifluoromethyl)-2*H*-1,4-benzoxazine: **^{1}H NMR**

(400MHz, $CDCl_3$) 7.87 (dd, 1H, J = 9.1, 2.8), 7.81 (d, 1H, J = 2.5), 6.92 (d, 1H, J = 9.1), 4.73 (d, 1H, J = 12.1), 4.48-4.39 (m, 1H), 4.13-4.06 (m, 2H), 3.99-3.88 (m, 1H).

(±)-7-Amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (Structure **34** of **Scheme VII**, where R^4 = trifluoromethyl, $R^x = CF_3$). This compound was prepared by General Method 4 (EXAMPLE 1) from (±)-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (45 mg, 0.16 mmol) and 10% Pd-C (30 mg) and purified by flash chromatography (EtOAc:hexanes, 1:1) to afford 26 mg (65%) of (±)-7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine. Data for (±)-7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine: **^{1}H NMR** (400MHz, $CDCl_3$) 6.68 (d, 1H, J = 8.4), 6.32-6.28 (m, 2H), 4.56 (dd, 1H, J = 12.0, 0.96), 4.16-4.00 (m, 2H), 3.84-3.69 (m, 2H), 3.60-3.32 (m, 2H).

(±)-1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **146A**, Structure **35** of **Scheme VII**, where R^1 = H, R^2, R^4 = trifluoromethyl, $R^x = CF_3$). This compound was prepared by General Method 11 (EXAMPLE 22) from (±)-7-amino-3,4-dihydro-4-(2,2,2-trifluoroethyl)-3-(trifluoromethyl)-2*H*-1,4-benzoxazine (26 mg, 0.11 mmol) and ethyl 4,4,4-trifluoroacetoacetate (58 mg, 0.32 mmol) in 1.5 mL toluene followed by treatment with 1 mL H_2SO_4 afforded 35 mg (90%) of Compound **146A**. Data for Compound **146A**: **^{1}H NMR** (400MHz, $CDCl_3$) 12.6 (broad s, 1H), 7.19 (broad s, 1H), 7.04 (s, 1H), 6.96 (s, 1H), 4.73 (d, 1H, J = 11.7), 4.42-4.31 (m, 1H), 4.23-4.19 (m, 1H), 4.02-3.95 (m, 1H), 3.96-3.84 (m, 1H).

EXAMPLE 43B

(+)-1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **146B**, Structure (+)-**35** of **Scheme VII**, where R^1 = H, R^2, R^4 = trifluoromethyl, $R^x = CF_3$) and (-)-1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **146C**, Structure (-)-**35** of **Scheme VIIA**, where R^1 = H, R^2, R^4 = trifluoromethyl, $R^x = CF_3$).

This compound was prepared according to General Method 9 (EXAMPLE 15) from Compound **146A** (EXAMPLE 42A) (10 mg, 0.03 mmol) on a semiprep Chiralpak AD column (20 x 250 mm) eluted hexanes/isopropanol (95:5), to afford 4.5 mg of Compound **146B**, an orange solid, and 4.7 mg of Compound **146C**, an orange solid. Data for Compound **146B**: HPLC (Chiralpak AD, 95:5 hexanes:isopropanol, 5.0 mL/min) t_R 54.1 min; $[\alpha]_D$ = +62.7.

Data for Compound **146C**: HPLC (Chiralpak AD, 95:5 hexanes:isopropanol, 5.0 mL/min) t_R 64.3 min; $[\alpha]_D$ = -60.4.

EXAMPLE 44

(±)-1-Ethyl-1,2,3,6-tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one (Compound **147**, Structure **35** of **Scheme VII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = Me, R^x = CH_3).

(±)-3,4-Dihydro-3-methyl-7-nitro-2*H*-1,4-benzoxazine (Structure **32** of **Scheme VII**, where R^4 = Me). This compound was prepared by General Method 17 (EXAMPLE 38) from 2-amino-5-nitrophenol (4.0 g, 25.9 mmol), chloroacetone (2.27 mL, 28.5 mmol), and K_2CO_3 (3.94 g, 28.5 mmol) to afford 3.5 g of crude solid. The crude solid (3.0 g, 14.2 mmol), $NaBH_3CN$ (892 mg, 14.2 mmol) and trifluoroacetic acid afforded 2.68 g (97%) of 3,4-dihydro-3-methyl-7-nitro-2*H*-1,4-benzoxazine. Data for (±)-3,4-dihydro-3-methyl-7-nitro-2*H*-1,4-benzoxazine: R_f 0.51 (2:3, EtOAc:hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, 1H, *J* = 8.7, 2.6), 7.70 (d, 1H, *J* = 2.3), 6.50 (d, 1H, *J* = 8.7), 4.46 (br s, 1H), 4.23 (dd, 1H, *J* = 10.5, 2.8), 3.76 (dd, 1H, *J* = 10.5, 7.8), 3.67 (m, 1H), 1.25 (d, 3H, *J* = 6.4).

(±)-4-Ethyl-3,4-dihydro-3-methyl-7-nitro-2*H*-1,4-benzoxazine (Structure **33** of **Scheme VII**, where R^4 = Me, R^x = CH_3). This compound was prepared by General Method 3 (EXAMPLE 1) from (±)-3,4-dihydro-3-methyl-7-nitro-2*H*-1,4-benzoxazine (200 mg, 1.0 mmol), acetaldehyde (455 mg, 10.3 mmol) and $NaBH_3CN$ (314 mg, 5.0 mmol) to afford 144 mg (63%) of 4-ethyl-3,4-dihydro-3-methyl-7-nitro-2*H*-1,4-

benzoxazine. Data for (±)-4-ethyl-3,4-dihydro-3-methyl-7-nitro-2*H*-1,4-benzoxazine: R_f 0.80 (3:2 EtOAc:hexanes); **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.80 (dd, 1H, *J* = 8.9, 2.6), 7.66 (d, 1H, *J* = 2.6), 6.55 (d, 1H, *J* = 9.2), 4.07 (dd, 1H, *J* = 10.7, 2.5), 3.96 (dd, 1H, *J* = 10.7, 2.6), 3.60 (m, 1H), 3.55-3.35 (m, 2H), 1.29 (d, 3H, *J* = 6.6), 1.24 (t, 3H, *J* = 7.0).

(±)-7-Amino-4-ethyl-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine (Structure **34** of **Scheme VII**, where R^4 = Me, R^x = CH_3). This compound was prepared by General Method 4 (EXAMPLE 1) from (±)-4-ethyl-3,4-dihydro-3-methyl-7-nitro-2*H*-1,4-benzoxazine (140 mg, 0.62 mmol) and purified by flash chromatography (EtOAc:hexanes, 3:2) to afford 90 mg (74%) of (±)-7-amino-4-ethyl-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine. Data for (±)-7-amino-4-ethyl-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine: R_f 0.48 (3:2 EtOAc:hexanes) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.53 (d, 1H, *J* = 8.0), 6.26-6.20 (m, 2H), 4.04 (dd, 1H, *J* = 10.5, 2.6), 3.94 (dd, 1H, *J* = 10.4, 4.3), 3.37-3.26 (m, 4H), 3.17-3.07 (m, 1H), 1.13 (m, 6H).

(±)-1-Ethyl-1,2,3,6-tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **147**, Structure **35** of **Scheme VII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = Me, R^x = CH_3). This compound was prepared by General Method 5 (EXAMPLE 1) from (±)-7-amino-4-ethyl-3,4-dihydro-3-methyl-2*H*-1,4-benzoxazine (90 mg, 0.47 mmol) and ethyl 4,4,4-trifluoroacetoacetate (103 mg, 0.56 mmol) and purified by flash chromatography (3:2 EtOAc:hexanes) to yield 46 mg (30%) of Compound **147**. Data for Compound **147**: R_f 0.37 (3:2, EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.07 (br s, 1H), 6.89 (s, 1H), 6.88 (s, 2H), 4.18 (dd, 1H, *J* = 10.5, 2.5), 4.09 (dd, 1H, *J* = 10.6, 3.4), 3.54-3.51 (m, 1H), 3.47-3.40 (m, 1H), 3.31-3.24 (m, 1H), 1.23 (m, 6H).

EXAMPLE 45

(2*R*)-(-)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-g]quinolin-7-one benzoxazine (Compound **148**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = Me, R^x = CF_3).

General Method 18: Displacement of a halonitroaromatic compound with an amino alcohol. A mixture of the halonitrobenzene (1.2 equiv) and the amino alcohol (1 equiv) was dissolved in absolute ethanol (3.3 M) or DMF. To this solution was added sodium bicarbonate (1 equiv). The suspension was heated at reflux temperature for 12 h when TLC indicated complete conversion of the amino alcohol. After cooling to room temperature, the reaction mixture was filtered with the aid of additional ethanol and the filtrate was concentrated under reduced pressure, which was then purified as indicated.

(2*R*)-(+)-2-(2-Fluoro-4-nitrophenyl)amino-1-propanol (Structure **36** of **Scheme VIII**, where R^4 = Me). This compound was prepared according to General Method 18 from 3,4-difluoronitrobenzene (76.2 g 0.48 mol), *R*-(+)-2-amino-1-propanol (30 g, 0.40 mol) and sodium bicarbonate (33.6 g, 0.40 mol) in 120 mL ethanol to afford 68.4g (80%) of (2*R*)-(+)-2-(2-fluoro-4-nitrophenyl)amino-1-propanol, a yellow solid, after recrystallization from ethanol. Data for (2*R*)-(+)-2-(2-fluoro-4-nitrophenyl)amino-1-propanol: mp 128.2-129.7 °C; $[\alpha]_D$ = + 22.6 (EtOH, *c* 3.1); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.99 (1H, dd, *J* = 11.4), 7.89 (1H, dd, *J* = 2.5, 11.6), 6.72 (1H, dd, *J* = 8.7), 4.75 (1H, bs), 3.8 (2H, m), 3.69 (1H, m), 1.31 (3H, d, *J* = 6.4).

General Method 19: Formation of an oxazolidine from an aminoalcohol and a carbonyl derivative, or its corresponding hydrate or hemiacetal. A r.b. flask equipped with a Dean-Stark condenser was charged sequentially with the amino alcohol (1 equiv), benzene (0.3 – 0.5 M), trifluoroacetaldehyde ethyl hemiacetal (5 equiv), and *p*-toluenesulfonic acid (catalytic). The reaction mixture was refluxed with azeotropic removal of water for 10-12 h. After cooling to room temperature the reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with aqueous sodium bicarbonate, brine and dried over anhydrous $MgSO_4$. After filtration, the solvents were removed under reduced pressure to afford the desired oxazolidine.

cis-(2*S*,4*R*)-(-)-3-(2-Fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine and *trans*-(2*R*,4*R*)-(+)-3-(2-Fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine (Structure **37 of Scheme VIII**, where R^4 = Me, R^x = CF_3). These compounds were prepared according to General Method 19 from (2*R*)-(+)-2-(2-fluoro-4-nitrophenyl)amino-1-propanol (68 g, 0.317 mole), 750 mL of benzene, trifluoroacetaldehyde ethyl hemiacetal (229 g, 1.58 mole), and 100 mg of *p*-toluenesulfonic acid (100 mg, 0.53 mmol) to afford *cis*-(2*S*,4*R*)-(-)-3-(2-fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine and *trans*-(2*R*,4*R*)-(+)-3-(2-fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine as a low melting solid. The product was found to be a mixture of two diastereoisomers (cis/trans 4:1). Crystallization from ethyl acetate-hexanes furnished the major (*cis*) isomer as pale yellow needles and the minor (*trans*) isomer as a glassy solid. The combined yield of both compounds was 93.2 g (100%).

Data for *cis*-(2*S*,4*R*)-(-)-3-(2-fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine: mp 46-50 °C; $[\alpha]_D$ = - 60.9 ($CHCl_3$, *c* 10.3); **^{1}H NMR** ($CDCl_3$) δ 8.01 (1H, m), 7.98 (1H, dd, *J* = 2.5, 12.3), 6.96 (1H, dd, *J* = 9.0), 5.75 (1H, q, *J* = 4.7), 4.33 (1H, m), 4.19 (1H, m), 3.99 (1H, m), 1.45 (3H, d, *J* = 6.26). Data for *trans*-(2*R*,4*R*)-(+)-3-(2-fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine: $[\alpha]_D$ = + 258.9 ($CHCl_3$, *c* 8.25); **^{1}H NMR** ($CDCl_3$) δ 8.02 (1H, dd), 7.98 (1H, dd, *J* = 2.5, 12.9). 6.96 (1H, dd, *J* = 8.5), 5.83 (1H, q, *J* = 4.7), 4.48 (1H, m), 4.40 (1H, m), 3.95 (1H, m), 1.23 (3H, d, *J* = 6.0).

(2*R*)-(-)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-propanol (Structure **38 of Scheme VIII**, where R^4 = Me, R^x = CF_3). A 1-L three-necked RB flask equipped with an addition funnel and mechanical stirrer was charged sequentially with *cis*-(2*S*,4*R*)-(-)-3-(2-fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine and *trans*-(2*R*,4*R*)-(+)-3-(2-fluoro-4-nitrophenyl)-4-methyl-2-trifluoromethyloxazolidine (93 g, 0.36 mole), 600 mL of dry chloroform, and triethylsilane (183.7 g, 1.58 mol). The solution was cooled to –78 °C and $TiCl_4$ (90 g, 0.474 mol) was added dropwise via addition funnel. After the addition was complete, the reaction mixture was allowed to warm to room temperature and stirred for another 24 h. The reaction mixture was quenched with ice and then neutralized with aqueous Na_2CO_3. The organic layers were washed with water,

brine and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate: hexanes 1: 9) to afford 57 g (61%) of (2*R*)-(-)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-propanol, as a glassy solid. Data for (2*R*)-(-)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-propanol $[\alpha]_D$ = - 205.9 (EtOH, *c* 10.15) ^{1}H NMR ($CDCl_3$) δ 7.99 (1H, dd, *J* = 2.5, 9.0), 7.95 (1H, dd, *J* = 2.6, 14,7), 7.32 (1H, dd, *J* = 8.6), 3.94 (1H, m), 3.74 (2H, m), 3.65 (1H, m), 1.86 (1H, bs), 1.19 (3H, d, *J* = 6.7).

General Method 20: Intramolecular cyclization of an alcohol of Structure **38** or **42** on a haloaromatic to form a benzoxazine. A solution of the aminoalcohol (1 equiv) in dry THF (1M) was added to a suspension of NaH (1.5 equiv) in dry THF (2M) and the mixture was heated at reflux. After cooling, methanol (50 mL/mol) was added to consume excess sodium hydride. The reaction mixture was poured into ice-cold water and extracted with ethyl acetate. The organic portions were combined, washed with brine and dried over $MgSO_4$. After filtration, the solvents were evaporated under reduced pressure and purified as indicated.

(3*R*)-(+)-3,4-Dihydro-3-methyl -7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **39** of **Scheme VIII**, where R^4 = Me, R^x = CF_3).

This compound was prepared according to General Method 20 from (2*R*)-(-)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-propanol (57 g, 0.193 mol) in 200 mL and NaH (6.93 g, 0.289 mole) in 400 mL of dry THF heated at reflux for 3 h to afford 36.5 g (68%) of (3*R*)-(+)-2,3-dihydro-3-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine, a yellow crystalline solid, after flash chromatography. Data for (3*R*)-(+)-2,3-dihydro-3-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: mp 95.5-96.4 °C; $[\alpha]_D$ = + 57.8 (EtOH, *c* 2.25); ^{1}H NMR ($CDCl_3$) δ 7.80 (1H, dd, *J* = 2.5, 9.1), 7.73 (1H, d, *J* = 2.6), 6.71 (1H, d, *J* = 9.1), 4.13 (2H, m), 4.03 (1H, m), 3.84 (1H, m), 3.69 (1H, m), 1.31 (3H, d *J* = 6.6).

(3*R*)-(-)-7-Amino-3,4-dihydro-3-methyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **40** of **Scheme VIII**, where R^4 = Me, R^x = CF_3). This compound was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-(+)-2,3-dihydro-3-methyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (35.5 g, 0.128 mol) and 10% palladium on carbon (3 g) in 400 mL of ethyl acetate to afford 31 g (98%) of (3*R*)-(-

)-7-amino-2,3-dihydro-3-methyl-4-trifluoroethyl-2*H*-1,4–benzoxazine, an off-white solid, after purification by silica gel column chromatography (ethyl acetate-hexanes). Data for (3*R*)-(-)-7-amino-2,3-dihydro-3-methyl-4-trifluoroethyl-2*H*-1,4–benzoxazine: $[\alpha]_D$ = - 39.4 (EtOH, *c* 1.7) **^{1}H NMR** ($CDCl_3$) δ 6.58 (1H, d, *J* = 8.2), 6.40 (1H, m), 6.37 (1H, m), 4.05 (1H, dd, *J* = 2.3, 11.0), 3.98 (1H, dd, *J* = 2.9, 10.6), 3.66 (2H, m), 3.38 (1H, m), 3.40 (NH2), 1.18 (3H, d, *J* = 6.6).

(2*R*-)-(-)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one benzoxazine (Compound **148**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = Me, R^x = CF_3).

A mixture of (3*R*)-(-)-7-amino-3,4-dihydro-3-methyl-4-trifluoroethyl-2*H*-1,4–benzoxazine (4.14 g, 16.8 mmol) and of ethyl 4,4,4-trifluoroacetoacetate (4.64 g, 25 mmol) were taken up in 85 mL of wet toluene (5% H_20). The reaction mixture was refluxed for 24 h. After cooling to room temperature, the solvents were evaporated under reduced pressure. The crude anilide obtained as a glassy solid was then treated with 50 mL of concentrated H_2SO_4. The reaction mixture was then slowly warmed to 70 °C and then to 98 °C. After 45 min, the heating bath was removed and the reaction mixture was allowed to cool to room temperature and then poured on to crushed ice with vigorous stirring. The yellow precipitate formed was filtered, washed with distilled water, and dried under vacuum. The crude product thus obtained was purified by silica gel column chromatography (ethyl acetate:hexanes), followed by recrystallization from ethyl acetate-hexanes to afford 2.6 g (42.3%) of Compound **148**, a bright-yellow crystalline solid. Data for Compound **148**: mp 219-223.1 °C; $[\alpha]_D$ = - 81.7 (EtOH, *c* 2.4); **^{1}H NMR** ($CDCl_3$) δ 7.05 (1H, s), 6.91 (1H, s), 6.89 (1H, s), 4.23 (1H, dd, *J* = 2.4, 10.8), 4.14 (1H, dd, *J* = 2.7, 10.7), 3.92 (1H, m), 3. 78 (1H, m), 3.61 (1H, m) 1.27 (3H, d *J* = 6.6).

EXAMPLE 46

(2*R*-)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **149**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = Et, R^x = CF_3).

(2*R*)-2-(2-Fluoro-4-nitrophenyl)amino-1-butanol (Structure **36** of **Scheme VIII**, where R^4 = Et). This compound was prepared according to General Method 18 (EXAMPLE 45) from 3,4-difluoronitrobenzene (5.34 mL, 0.048 mol), *R*-(-)-2 amino-1-butanol (4.14 mL, 0.044 mol) and sodium bicarbonate (3.68 g, 0.044 mol) in 133 mL anhydrous DMF heated at 90 °C for 12 hrs to afford 9.9 g (99%) of (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-1-butanol, a yellow oil, after flash chromatography (gradient elution, hexanes:ethyl acetate 95:5 to 50:50). Data for (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-1-butanol: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.8, 1.5, 1H), 7.89 (dd, J = 11.7, 2.4, 1H), 6.71 (dd, J = 8.8, 8.8, 1H), 4.72 (bs, 1H), 3.81 (m, 1H), 3.73 (m, 1H), 3.55 (m, 1H), 1.76 (m, 1H), 1.63 (m, 1H), 1.02 (t, J = 7.8, 3H).

(4*R*)-3-(2-Fluoro-4-nitrophenyl)-4-ethyl-2-(trifluoromethyl)-1,3-oxazolidine (Structure **37** of **Scheme VIII**, where R^4 = Et, R^x = CF_3). This compound was prepared according to General Method 19 (EXAMPLE 45) from (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-1-butanol (1.6 g, 70 mmol), trifluoroacetaldehyde ethyl hemiacetal (4.9 g, 34 mmol) and *p*-toluenesulfonic acid (0.13 g, 0.68 mmol) in 70 mL anhydrous benzene to afford 1.8 g (85%) of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-ethyl-2-trifluoromethyloxazolidine, after flash chromatography (gradient elution, hexanes:ethyl acetate 90:10 to 50:50). Data for (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-ethyl-2-trifluoromethyloxazolidine: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (m, 1H), 7.98 (m, 1H), 6.95 (dd, J = 8.8, 8.8, 1H), 5.68 (m, 1H), 4.30 (m, 1H), 4.08 (m, 1H), 3.92 (m, 1H), 2.00 (m, 1H), 1.67 (m, 1H), 0.97 (t, J = 7.8, 3H).

(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol (Structure **38** of **Scheme VIII**, where R^4 = Et, R^x = CF_3). To a solution of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-ethyl-2-trifluoromethyloxazolidine (9.2 g, 29.8 mmol) and Et_3SiH (19.1 mL, 119 mmol) in 100 mL chloroform was added BF_3OEt_2 (7.56 mL, 60 mmol). The reaction was heated to reflux for 12 hrs, whereupon additional BF_3OEt_2 (7.56 mL, 60

mmol) was added, and the mixture heated at reflux for an additional 12 hrs. After cooling, MeOH (5 mL) was added and the reaction was allowed to stir at r.t. for an hour. The reaction was poured in water (250 mL) and extracted with ethyl acetate (3 x 250 mL). The organic layers were combined, washed sequentially with water (250 mL) and brine (250 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a brown oil. Flash chromatography (gradient elution, hexanes:ethyl acetate 95:5 to 50:50) afforded 5.4 g (59%) of (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol. Data for (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.98 (dd, J = 8.8, 2.4, 1H), 7.94 (dd, J = 13.2, 2.9, 1H), 7.37 (dd, J = 8.8, 8.8, 1H), 4.12 (m, 1H), 3.87 (m, 1H), 3.77 (m, 1H), 3.70 (m, 1H), 3.57 (m, 1H), 1.78 (dd, J = 6.8, 4.4, 1H), 1.58 (dq, J = 7.8, 2.9, 2H), 0.95 (t, J = 7.3, 1H).

(3*R*)-3-Ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **39 of Scheme VIII**, where R^4 = Et, R^x = CF_3). This compound was prepared according to General Method 20 from (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-1-butanol (5.4 g, 17.3 mmol) in 45 mL THF and NaH (1.4 g, 35 mmol) in 10 mL THF heated at reflux for 1 hr to afford 3.78g (75%) of (3*R*)-3-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine, after flash chromatography (gradient elution, hexanes:ethyl acetate 95:5 to 50:50). Data for (3*R*)-3-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (dd, J = 8.8, 2.4, 1H), 7.73 (d, J = 2.9, 1H), 6.72 (d, J = 8.8, 1H), 4.34 (dd, J = 11.2, 1.5, 1H), 4.13 (m, 1H), 4.03 (dd, J = 11.2, 2.4, 1H), 3.8 (m, 1H), 3.37 (m, 1H), 1.67 (m, 1H), 1.01 (t, J = 7.3, 3H).

(3*R*)-7-Amino-3-ethyl-3,4-dihydro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **40 of Scheme VIII**, where R^4 = Me, R^x = CF_3). This compound was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3-ethyl-3,4-dihydro-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (5.6 g, 19.3 mmol) and 10% Pd/C (cat.) in 60 mL ethyl acetate to afford 4.8 g (95%) of (3*R*)-7-amino-3,4-dihydro-3-ethyl-4-trifluoroethyl-2*H*-1,4–benzoxazine as a tan solid, which was carried on directly to the next step.

(2*R*)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **149**, Structure **41** of **Scheme VIII**, where

R^1 = H, R^2 = trifluoromethyl, R^4 = Et, R^x = CF_3). This compound was prepared by General Method 11 (EXAMPLE 22) from (3*R*)-7-amino-3-ethyl-3,4-dihydro-4-trifluoroethyl-2*H*-1,4–benzoxazine (4.8 g, 18.4 mmol) and ethyl-4,4,4-trifluoroacetoacetate (8.1 mL, 55.2 mmol) in 58 mL toluene heated at reflux for 3d, followed by workup and treatment with 35 mL concentrated H_2SO_4 heated to 90 ^{0}C for 0.5 h to afford 1.5 g (21%) of Compound **149**, a yellow solid, after flash chromatography (gradient elution, hexanes:ethyl acetate 95:5 to 50:50) followed by additional purification using reverse phase HPLC (Kromasil C18, 50 x 250 mm; 65:35 MeOH:water; flow rate of 80 mL/min.). Data for Compound **149**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.75 (bs, 1H), 7.06 (s, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 6.89 (s, 1H), 4.34 (dd, J = 10.7, 1.5, 1H), 4.14 (dd, J = 11.2, 2.4, 1H), 3.99 (m, 1H), 3.75 (m, 1H), 3.28 (m, 1H), 1.64 (dq, J = 7.6, 7.3, 2H), 1.00 (t, J = 7.3, 3H).

EXAMPLE 47

(2*R*)-1,2,3,6-Tetrahydro-2-isobutyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **150**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = isobutyl, R^x = CF_3).

(2*R*)-2-(2-Fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol (Structure **36** of **Scheme VIII**, where R^4 = isobutyl). This compound was prepared according to General Method 18 (EXAMPLE 45) from 3,4-difluoronitrobenzene (8.73 g, 54.9 mmol), *R*-2-amino-4-methyl-1-pentanol (5.00 g, 42.7 mmol) in EtOH heated at reflux for 16 h to afford 6.0 g (55%) of (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol, a yellow solid, after flash chromatography (gradient elution, hexanes:EtOAc 9:1 to 1:1). Data for (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-4-methyl-1-pentanol: R_f 0.3 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.01-7.97 (m, 1H), 7.90 (dd, 1H, *J* = 11.7, 2.7), 6.74 (dd, 1H, *J* = 8.6, 8.6), 4.62-4.57 (m, 1H), 3.82-3.74 (m, 1H), 3.75-3.62 (m, 2H), 1.77-1.65 (m, 1H), 1.61-1.45 (m, 2H), 0.99 (d, 3H, *J* = 6.6), 0.93 (d, 3H, *J* = 6.6).

(4*R*)-3-(2-Fluoro-4-nitrophenyl)-4-isobutyl-2-(trifluoromethyl)-1,3-oxazolidine (Structure **37** of **Scheme VIII**, where R^4 = isobutyl, R^x = CF_3. This compound was prepared according to General Method 19 (EXAMPLE 45) from (2*R*)-2-(2-fluoro-4-

nitrophenyl)amino-4-methyl-1-pentanol (6.0 g, 23 mmol) trifluoroacetaldehyde ethyl hemiacetal (30.4 g, 211 mmol) and *p*-toluenesulfonic acid (0.020 g, 0.10 mmol) in 250 mL benzene to afford 5.15 g (65%) of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isobutyl-2-trifluoromethyloxazolidine. Data for (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isobutyl-2-trifluoromethyloxazolidine as a mixture of diastereomers: R_f 0.8 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.03-7.94 (m, 2H), 6.96-6.88 (m, 1H), 5.81 (q, 1H, minor diast., J = 4.7), 5.69 (q, 1H, major diast., J = 4.7), 4.45-4.40 (m, 1H, minor diast.), 4.36-4.28 (m, 1H, major diast.), 4.11-4.01 (m, 2H), 1.82-1.74 (m, 1H), 1.66-1.52 (m, 2H), 1.02 (d, 3H, major diast., J = 6.4), 0.99-0.95 (m, 3H), 0.91 (d, 3H, minor diast., J = 6.6).

(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol (Structure **38** of **Scheme VIII**, where R^4 = isobutyl, R^x = CF_3. To a solution of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isobutyl-2-trifluoromethyloxazolidine (4.8 g, 14.3 mmol) and Et_3SiH (21.6 g, 186 mmol) in 60 mL chloroform was added BF_3OEt_2 (14.2, 60 mmol, added in portions) The reaction was heated at reflux for 1 d After cooling, the reaction was poured in water (200 mL) and extracted with chloroform (3 x 150 mL). The organic layers were combined, washed sequentially with water (200 mL) and brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to a brown oil. Flash chromatography (gradient elution, hexanes:ethyl acetate 95:5 to 3:1) afforded 2.1 g (44%) of (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol, an orange oil. Data for (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol: R_f 0.8 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.98 (dd, 1H, J = 9.3, 2.4), 7.94 (dd, 1H, J = 12.9, 2.5), 7.40 (dd, 1H, J = 8.7, 8.7), 4.21-4.10 (m, 1H), 3.89-3.78 (m, 1H), 3.79-3.65 (m, 3H), 1.96-1.89 (m, 1H), 1.67-1.54 (m, 1H), 1.55-1.44 (m, 1H), 1.32-1.22 (m , 1H), 0.91 (d, 3H, J = 6.6), 0.77 (d, 3H, J = 6.6).

(3*R*)-3,4-Dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **39** of **Scheme VIII**, where R^4 = isobutyl, R^x = CF_3. This compound was prepared according to General Method 20 (EXAMPLE 45) from (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-4-methyl-1-pentanol (1.95 g, 5.76 mmol) in 30 mL THF and NaH (1.4 g, 35 mmol) in 25 mL THF heated at reflux for 1 hr to afford 0.87 g (50%) of (3*R*)-3,4-dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-

benzoxazine, a yellow oil. Data for (3*R*)-3,4-dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.6 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.79 (dd, 1H, *J* = 9.1, 2.7), 7.71 (d, 1H, *J* = 2.5), 6.72 (d, 1H, *J* = 9.1), 4.30 (dd, 1H, ABx, *J* = 11.0, 1.5), 4.19-4.06 (m, 1H), 4.06-4.01 (m, 1H), 3.82-3.73 (m, 1H), 3.53-3.47 (m, 1H), 1.71-1.61 (m, 2H), 1.38-1.29 (m, 1H), 0.99 (d, 3H, *J* = 6.5), 0.96 (d, 3H, *J* = 6.5).

(3*R*)-7-Amino-3,4-dihydro-3-isobutyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **40** of **Scheme VIII**, where R^4 = isobutyl, R^x = CF_3). This compound was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3,4-dihydro-3-isobutyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (0.22 g, 0.69 mmol) and 10% Pd/C (0.075 g) in 5 mL ethyl acetate to afford 0.13 g (65%) of (3*R*)-7-amino-3,4-dihydro-3-isobutyl-4-trifluoroethyl-2*H*-1,4-benzoxazine. Data for (3*R*)-7-amino-3,4-dihydro-3-isobutyl-4-trifluoroethyl-2*H*-1,4-benzoxazine: R_f 0.3 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.63 (d, 1H, *J* = 8.5), 6.27 (dd, 1H, *J* = 8.5, 2.6), 6.23 (d, 1H, *J* = 2.5), 4.10 (dd, 1H, ABx, *J* = 10.6, 1.8), 3.97 (dd, 1H, ABx, *J* = 10.6, 2.3), 3.70-3.51 (m, 2H), 3.38 (broad s, 2H), 3.19-3.13 (m, 1H), 1.75-1.63 (m, 1H), 1.47-1.25 (m, 2H), 0.93 (d, 3H, *J* = 6.6), 0.89 (d, 3H, *J* = 6.6).

(2*R*)-1,2,3,6-Tetrahydro-2-isobutyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **150**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = isobutyl, R^x = CF_3). This compound was prepared by General Method 11 (EXAMPLE 22) from (3*R*)-7-amino-3,4-dihydro-3-isobutyl-4-trifluoroethyl-2*H*-1,4-benzoxazine (0.13 g, 0.45 mmol) and ethyl-4,4,4-trifluoroacetoacetate (0.25 g, 1.4 mmol) in 6 mL toluene heated at reflux for 3h, followed by workup and treatment with 3 mL concentrated H_2SO_4 heated to 95 ^{0}C for 1 h to afford 17 mg (9%) of Compound **150**, a yellow solid, after purification by flash chromatography (95:5 CH_2Cl_2:MeOH) and recrystallization from EtOAc:hexanes. Data for Compound **150**: R_f 0.2 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.58 (broad s, 1H), 7.05 (broad s, 1H), 6.97 (s, 1H), 6.91 (s, 1H), 4.30 (dd, 1H, *ABX*, *J* = 11.0, 1.1), 4.16 (dd, 1H, *ABX*, *J* = 11.0, 1.3), 4.01-3.91 (m, 1H), 3.75-3.65 (m, 1H), 3.42-3.37 (m, 1H), 1.71-

1.62 (m, 1H), 1.62-1.54 (m, 1H), 1.35-1.27 (m, 1H), 0.96 (d, 3H, J = 6.9), 0.93 (d, 3H, J = 7.5).

EXAMPLE 48

(2*R*)-1,2,3,6-Tetrahydro-2-isopropyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **151**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = isopropyl, R^x = CF_3).

(2*R*)-2-(2-Fluoro-4-nitrophenyl)amino-3-methyl-1-butanol (Structure **36** of **Scheme VIII**, where R^4 = isopropyl). This compound was prepared according to General Method 18 (EXAMPLE 45) from 3,4-difluoronitrobenzene (9.9 g, 62 mmol), *R*-2-amino-3-methyl-1-butanol (5.00 g, 48.5 mmol) in 6 mL EtOH heated at reflux for 22 h to afford 8.3 g (71%) of (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-3-methyl-1-butanol, a yellow solid, after flash chromatography. Data for (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-3-methyl-1-butanol: R_f 0.8 (1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.00-7.96 (m, 1H), 7.90 (dd, 1H, J = 11.6, 2.4), 6.73 (dd, 1H, J = 8.5, 8.5), 4.75-4.69 (m, 1H), 3.87-3.79 (m, 1H), 3.79-3.70 (m, 1H), 3.47-3.39 (m, 1H), 2.06-1.97 (m, 1H), 1.03 (d, 3H, J = 3.6), 1.01 (d, 3H, J = 3.6).

(4*R*)-3-(2-Fluoro-4-nitrophenyl)-4-isopropyl-2-(trifluoromethyl)-1,3-oxazolidine (Structure **37** of **Scheme VIII**, where R^4 = isopropyl, R^x = CF_3. This compound was prepared according to General Method 19 (EXAMPLE 45) from (2*R*)-2-(2-fluoro-4-nitrophenyl)amino-3-methyl-1-butanol (8.3 g, 34 mmol) trifluoroacetaldehyde ethyl hemiacetal (86.4 g, 0.600 mol) and *p*-toluenesulfonic acid (20 mg, 0.10 mmol) in 220 mL benzene to afford 5.2 g (47%) of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isopropyl-2-trifluoromethyloxazolidine. Data for (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isopropyl-2-trifluoromethyloxazolidine: R_f 0.7 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.04-7.97 (m, 2H), 7.22 (dd, 1H, J = 8.7, 8.7), 5.34 (quartet, 1H, J = 4.6), 4.27 (dd, 1H, J = 8.0, 8.0), 4.11(dd, 1H, J = 7.4, 7.4), 3.81 (quartet, 1H, J = 7.1), 2.02-1.93 (m, 1H), 0.96 (d, 6H, J = 6.8).

(2*R*)-2-[2-Fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-3-methyl-1-butanol (Structure **38** of **Scheme VIII**, where R^4 = isopropyl, R^x = CF_3. To a solution of (4*R*)-3-(2-fluoro-4-nitrophenyl)-4-isopropyl-2-trifluoromethyloxazolidine (1.8 g, 5.6 mmol) and

Et_3SiH (1.88 g, 16.1 mmol) in 15 mL $CHCl_3$ was added $TiCl_4$ (6 mL of a 1M solution in CH_2Cl_2, 6 mmol) at –78 °C. The solution was stirred for 2 h, then allowed to warm to 0 °C and stirred for 2h. The mixture was poured into 150 mL water and neutralized with 6N NaOH. The aqueous layer was extracted with $CHCl_3$ (3 x 100 mL), and the combined organic layers washed with brine (150 mL), dried over $MgSO_4$, filtered and concentrated. Flash chromatography (gradient elution, hexanes:EtOAc 9:1 to 3:1) afforded 1.6 g (88%) of (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-3-methyl-1-butanol, an orange oil. Data for (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-3-methyl-1-butanol: R_f 0.3 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.96 (dd, 1H, *J* = 8.8, 2.3), 7.92 (dd, 1H, *J* = 13.4, 2.5), 7.37 (dd, 1H, *J* = 8.8, 8.8), 4.33-4.23 (m, 1H), 4.03-3.86 (m, 2H), 3.81-3.74 (m, 1H), 3.36-3.27 (m, 1H), 1.97-1.88 (m, 1H), 1.85 (broad s, 1H), 0.99 (d, 3H, *J* = 6.6), 0.94 (d, 3H, *J* = 6.6).

(3*R*)-3,4-Dihydro-3-isopropyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **39 of Scheme VIII**, where R^4 = isopropyl, R^x = CF_3. This compound was prepared according to General Method 20 (EXAMPLE 45) from (2*R*)-2-[2-fluoro-4-nitro(2,2,2-trifluoroethyl)anilino]-3-methyl-1-butanol (1.58 g, 4.87 mmol) in 30 mL THF and NaH (0.351 g, 14.6 mmol) in 10 mL THF heated at reflux for 0.5 hr to afford 0.80 g (54%) of (3*R*)-3,4-dihydro-3-isopropyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine, a yellow oil, after purification by flash chromatography (gradient elution, hexanes:EtOAc 9:1 to 3:1). Data for (3*R*)-3,4-dihydro-3-isopropyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine: R_f 0.5 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.81 (dd, 1H, *J* = 9.1, 2.5), 7.72 (d, 1H, *J* = 2.6), 6.79 (d, 1H, *J* = 9.1), 4.49 (dd, 1H, *ABX*, *J* = 11.1, 0.92), 4.37-4.26 (m, 1H), 3.95 (dd, 1H, *J* = 11.1, 2.4), 3.80-3.69 (m, 1H), 3.14 (d, 1H, *J* = 8.5), 2.08-1.98 (m, 1H), 1.01 (d, 3H, *J* = 6.9), 0.99 (d, 3H, *J* = 6.9).

(3*R*)-7-Amino-3,4-dihydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (Structure **40 of Scheme VIII**, where R^4 = isopropyl, R^x = CF_3). This compound was prepared according to General Method 4 (EXAMPLE 1) from (3*R*)-3,4-dihydro-3-isopropyl-7-nitro-4-(2,2,2-trifluoroethyl)-2*H*-1,4-benzoxazine (0.350 g, 1.15 mmol) and 10% Pd/C (0.14 g) in 7 mL EtOAc to afford 0.284 g (90%) of (3*R*)-7-amino-

3,4-dihydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4–benzoxazine after purification by flash chromatography (gradient elution, hexanes:EtOAc 9:1 to 3:1). Data for (3*R*)-7-amino-3,4-dihydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4–benzoxazine: R_f 0.2 (3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.71 (d, 1H, *J* = 8.5), 6.27 (dd, 1H, *J* = 8.5, 2.6), 6.20 (d, 1H, *J* = 2.5), 4.34 (dd, 1H, *ABX*, *J* = 11.0, 1.5), 3.84 (dd, 1H, *ABX*, *J* = 11.3, 2.2), 3.71-3.47 (m, 2H), 3.41 (broad s, 2H), 2.62 (d, 1H, *J* = 9.8), 1.81-1.70 (m, 1H), 0.98 (d, 3H, *J* = 6.7), 0.96 (d, 3H, *J* = 6.7).

(2*R*)-1,2,3,6-Tetrahydro-2-isopropyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one (Compound **151**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4 = isopropyl, R^x = CF_3). This compound was prepared according to General Method 11 (EXAMPLE 22) from (3*R*)-7-amino-3,4-dihydro-3-isopropyl-4-(2,2,2-trifluoroethyl)-2*H*-1,4–benzoxazine (0.284 g, 1.04 mmol) and ethyl 4,4,4-trifluoroacetoacetate (0.573 g, 3.11 mmol) in 8 mL toluene followed by workup and treatment with 6 mL conc. sulfuric acid to afford 0.15 g (38%) of Compound **151**, a yellow solid, after flash chromatography (19:1 CH_2Cl_2:MeOH). Further purification was performed by reverse phase HPLC (ODS, 5 microm, 10 x 250 mm), 80% MeOH:water, 2.6 mL/min). Data for Compound **151**: R_f 0.2 (19:1 CH_2Cl_2:MeOH); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 12.52 (broad s, 1H), 7.14 (broad s, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 4.50 (d, 1H, *J* = 11.0), 4.18-4.06 (m, 1H), 4.05 (dd, 1H, *ABX*, *J* = 11.0, 2.5), 3.75-3.60 (m, 1H), 2.98 (d, 1H, *J* = 8.7), 1.98-1.88 (m, 1H), 1.00 (d, 3H, *J* = 7.3), 0.98 (d, 3H, *J* = 7.3).

EXAMPLE 49

(±)-1,2,3,4,4a,5-Hexahydro-11-(trifluoromethyl)-pyrido[1',2':4,5][1,4]oxazino[3,2-g]quinolin-9(8*H*)-one (Compound **152**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4, R^x = –$(CH_2)_3$–).

(±)-[1-(2-Fluoro-4-nitrophenyl)-2-piperidinyl]-methanol] (Structure **42** of **Scheme IX**, where R^4, R^x = –$(CH_2)_4$–). A solution of 3,4-difluoronitrobenzene (1.00 g, 6.28 mmol) and (±)-2-piperidinemethanol (0.724 g, 6.28 mmol) in 1.5 mL EtOH was heated at 50 °C for 18h, then heated at reflux for 24 h. The solvent was concentrated and

the crude reaction purified by flash chromatography (7:3 hexanes:EtOAc) to afford 0.85 g (53%) of (±)-[1-(2-fluoro-4-nitrophenyl)-2-piperidinyl]-methanol], an orange oil. Data for (±)-[1-(2-fluoro-4-nitrophenyl)-2-piperidinyl]-methanol]: R_f 0.36 (3:7, EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.95 (dd, 1H, J = 8.8, 2.4), 7.88 (dd, 1H, J = 13.2, 2.4), 7.01 (t, 1H, J = 8.8), 4.04-3.97 (m, 2H), 3.74-3.68 (m, 1H), 3.45-3.42 (m, 1H), 3.34-3.28 (m, 1H), 1.89-1.82 (m, 1H), 1.77-1.61 (m, 6H).

(±)-3-Nitro-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine (Structure **39** of **Scheme IX**, where R^4, R^x = – $(CH_2)_4$–). A suspension of (±)-[1-(2-fluoro-4-nitrophenyl)-2-piperidinyl]-methanol (0.586 g, 2.30 mmol) and sodium hydride (60% mineral oil suspension, 0.101 g, 2.54 mmol) in 10 mL THF was heated at reflux for 16 h. The mixture was neutralized with phosphate buffer (pH 7), and the resultant solution was extracted twice with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (7:3 hexanes:EtOAc) afforded 0.410 g (76%) of (±)-3-nitro-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine, a yellow-orange solid. Data for (±)-3-nitro-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine: R_f 0. 71 (2:3, EtOAc:hexanes) **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.78 (dd, 1H, J = 9.3, 2.9), 7.64 (d, 1H, J = 2.9), 6.75 (d, 1H, J = 9.3), 4.23 (dd, 1H, J = 10.7, 2.9), 3.96 (dd, 1H, J = 10.7, 7.8), 3.93 (m, 1H), 3.22-3.17 (m, 1H), 2.78 (td, 1H, J = 12.8, 3.0), 1.95-1.92 (m, 1H), 1.88-1.84 (m, 1H), 1.75-1.71 (m, 1H), 1.66-1.60 (m, 1H), 1.58-1.48 (m, 1H), 1.35-1.27 (m, 1H).

(±)-3-Amino-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine (Structure **40** of **Scheme VIII**, where R^4, R^x = – $(CH_2)_3$–). This compound was prepared according to General Method 4 (EXAMPLE 1) from (±)-3-nitro-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine (0.300 g, 1.30 mmol) to afford 0.232 g (88%) of (±)-3-amino-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine, a colorless oil, after flash chromatography (gradient elution 3:7 EtOAc:hexanes, then 3:2 EtOAc: hexanes). Data for (±)-3-amino-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine: R_f 0.5 (2:3, EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.66 (d, 1H, J = 8.3), 6.24 (dd, 1H, J =

8.5, 2.7), 6.21 (d, 1H, J = 2.4), 4.11 (dd, 1H, J = 10.7, 2.4), 3.97 (dd, 1H, J = 10.7, 9.0), 3.69 (dd, 1H, J = 13.7, 11.2), 3.33 (br s, 2H), 2.85-2.80 (m, 1H), 2.43 (td, 1H, J = 11.7, 2.9), 1.87-1.78 (m, 2H), 1.69-1.60 (m, 2H), 1.45-1.36 (m, 1H), 1.28-1.19 (m, 1H).

(±)-1,2,3,4,4a,5-Hexahydro-11-(trifluoromethyl)-pyrido[1',2':4,5][1,4]oxazino[3,2-g]quinolin-9(8*H*)-one (Compound **152**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4, R^x = – $(CH_2)_3$ –). This compound was prepared according to General Method 11 (EXAMPLE 22) from (±)-3-amino-6,6a,7,8,9,10-hexahydropyrido[2,1-*c*][1,4]benzoxazine (0.232 g, 1.13 mmol), ethyl 4,4,4-trifluoroacetoacetate (0.250 g, 1.36 mmol) in 11 mL benzene followed by treatment with conc. H_2SO_4 to afford 0.110 g (30%) of Compound **152**, a yellow fluffy solid. Data for Compound **152**: R_f 0.15 (2:3, EtOAc:hexanes); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.73 (br s, 1H), 7.09 (s, 1H), 6.87 (s, 1H), 6.73 (s, 1H), 4.26 (dd, 1H, J = 10.5, 2.6), 4.06 (dd, 1H, J = 10.5, 9.0), 3.80 (m, 1H), 3.02-2.97 (m, 1H), 2.60 (td, 1H, J = 12.2, 2.9), 1.92 (m, 2H), 1.74-1.65 (m, 2H), 1.50-1.42 (m, 1H), 1.29-1.21 (m, 1H).

EXAMPLE 50

(*R*)-2,3,3a,4-Tetrahydro-10-(trifluoromethyl)-1*H*-pyrrolo[1',2':4,5][1,4]oxazino[3,2-*g*]quinolin-8(7*H*)-one (Compound **153**, Structure **41** of **Scheme VIII**, where R^1 = H, R^2 = trifluoromethyl, R^4, R^x = – $(CH_2)_2$ –).

(*R*)-[1-(2-Fluoro-4-nitrophenyl)-2-pyrrolidinyl]-methanol (Structure **42** of **Scheme IX**, where R^4, R^x = – $(CH_2)_2$ –). A suspension of 3,4-difluoronitrobenzene (1.57 g, 9.8 mmol), (*R*)-2-pyrrolidinemethanol (1.0 g, 9.8 mmol) and K_2CO_3 (1.36 g, 9.8 mmol) in 30 mL DMF was heated at 75 °C for 20h, whereupon the mixture was partitioned between water (100 mL) and EtOAc (100 mL). The aqueous layer was extracted with EtOAc (100 mL), and the combined organic layers washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography (19:1 CH_2Cl_2:MeOH) afforded 2.27 g (96%) of (*R*)-[1-(2-fluoro-4-nitrophenyl)-2-pyrrolidinyl]-methanol, an orange solid. Data for (*R*)-[1-(2-fluoro-4-nitrophenyl)-2-

pyrrolidinyl]-methanol: R_f 0.17 (7:3 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.94 (dd, 1H, *J* = 9.1, 2.6), 7.89 (dd, 1H, *J* = 14.4, 2.6), 6.68 (t, 1H, *J* = 9.0), 4.25-4.32 (m, 1H), 3.60-3.75 (m, 3H), 3.40-3.50 (m, 1H), 1.95-2.15 (m, 4H), 1.43 (t, 1H, *J* = 5.8).

(*R*)-2,3,3a,4-Tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (Structure **42** of **Scheme IX**, where R^4, R^X = – $(CH_2)_2$ –). A suspension of (*R*)-[1-(2-fluoro-4-nitrophenyl)-2-pyrrolidinyl]-methanol (2.27 g, 9.4 mmol) and NaH (60% mineral oil suspension, 0.737 g, 18.9 mmol) in 35 mL THF was heated at reflux for 1h. The reaction was quenched with phosphate buffer, and the aqueous layer was extracted with EtOAc. The solution was filtered through Celite, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (3:2 EtOAc:hexanes) afforded 476 mg (22%) of (*R*)-2,3,3a,4-tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine, an orange solid. Data for (*R*)-2,3,3a,4-tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine: R_f 0.55 (3:2 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (dd, 1H, *J* = 9.2, 2.4), 7.74 (d, 1H, *J* = 2.4), 6.44 (d, 1H, *J* = 8.8), 4.56 (dd, 1H, *J* = 10.3, 3.4), 3.65-3.72 (m, 1H), 3.60 (broad t, 1H, *J* = 8.6), 3.44 (t, 1H, *J* = 10.0), 3.36 (td, 1H, *J* = 9.8, 7.3), 2.15-2.25 (m, 2H), 2.05-2.15 (m, 1H), 1.45-1.55 (m, 1H).

(*R*)-7-Amino-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (Structure **40** of **Scheme VIII**, where R^4, R^X = – $(CH_2)_2$ –). This compound was prepared according to General Method 4 (EXAMPLE 1) from (*R*)-2,3,3a,4-tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (0.470 g, 2.10 mmol) to afford 0.39 g (98%) of (*R*)-2,3,3a,4-tetrahydro-7-nitro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine. Data for (*R*)-7-amino-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine: R_f 0.55 (3:2 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.50 (d, 1H, *J* = 8.3), 6.32 (d, 1H, *J* = 2.4), 6.29 (dd, 1H, *J* = 8.3, 2.4), 4.31 (dd, 1H, *J* = 8.3, 1.5), 3.37-3.50 (m, 3H), 3.31 (broad s, 2H), 3.13 (broad q, 1H, *J* = 8.3), 2.07-2.15 (m, 1H), 1.90-2.05 (m, 2H), 1.40-1.50 (m, 1H).

(*R*)-2,3,3a,4-Tetrahydro-10-(trifluoromethyl)-1H-pyrrolo[1',2':4,5][1,4]oxazino[3,2-g]quinolin-8(7*H*)-one (Compound **153**, Structure **41** of

Scheme VIII, where R^1 = H, R^2 = trifluoromethyl, R^4, R^x = $-(CH_2)_2-$). This compound was prepared according to General Method 11 (EXAMPLE 22) from (*R*)-7-amino-2,3,3a,4-tetrahydro-1*H*-pyrrolo[2,1-*c*][1,4]benzoxazine (0.390 g, 2.05 mmol) and ethyl 4,4,4-trifluoroacetoacetate (0.378 g, 2.05 mmol) in 14 mL benzene, followed by workup and treatment with 7 mL concentrated sulfuric acid to afford 120 mg (20%) of Compound **153**, a yellow solid after flash chromatography (92:8 CH_2Cl_2:MeOH). Further purification was performed by reverse phase HPLC (ODS, 5 micron, 10 x 250 mm, 3 mL/min). Data for Compound **153**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.42 (broad s, 1H), 6.91 (s, 1H), 6.89 (s, 1H), 6.76 (broad s, 1H), 4.54 (dd, 1H, *J* = 9.6, 2.7), 3.61 (t, 1H, *J* = 9.6), 3.50-3.60 (m, 1H), 3.40-3.50 (m, 1H), 3.30-3.40 (m, 1H), 2.12-2.22 (m, 2H), 2.00-2.10 (m, 1H), 1.40-1.50 (m, 1H).

EXAMPLE 51

1,3,4,6-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-g]quinolin-2,7-dione (Compound **154**, Structure **47** of **Scheme X**, where R^1 = H, R^2 = trifluoromethyl, R^6 = R^7 = R^{13} = Me).

3,4-Dihydro-3,3-dimethylquinoxalin-2(1*H*)-one (Structure **44** of **Scheme X**, where R^6 = R^7 = Me). In a 200-mL r.b. flask, a solution of 1,2-phenylenediamine (2.12 g, 19.6 mmol), diisopropylethylamine (4.55 ml, 25.5 mmol, 1.3 equiv), ethyl-2-bromoisobutyrate (4.97 mL, 25.5 mmol, 1.3 equiv) in DMF (20 mL) was heated to 110 °C overnight, cooled, partitioned between EtOAc (100 mL) and H_2O (30 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed sequentially with 1 M HCl (40 mL), H_2O (40 mL), saturated $NaHCO_3$ (40 ml), H_2O (40 mL) and brine (30 mL), dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by recrystallization (CH_2Cl_2/hexane) to give 2.09 g (60%) of 3,4-dihydro-3,3-dimethylquinoxalin-2(1*H*)-one as white crystals. Data for 3,4-dihydro-3,3-dimethylquinoxalin-2(1*H*)-one: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.84 (bs, 1H), 6.89 (dd, *J* = 7.3, 7.3, 1H), 6.76 (dd, *J* = 7.2, 7.3, 1H), 6.70 (d, *J* = 7.6, 1H), 6.67 (d, *J* = 6.9, 1H), 3.69 (bs, 1H), 1.41 (s, 6H).

3,4-Dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one. In a 200-mL r.b. flask, a solution of 3,4-dihydro-3,3-dimethylquinoxalin-2(1*H*)-one (1.00 g, 5.66 mmol) in dry THF was treated with NaH (0.28 g, 7.09 mmol, 1.25 equiv). The reaction mixture was stirred at room temperature for 30 minutes before iodomethane (0.39 mL, 6.24 mmol, 1.1 equiv) was added to the reaction flask. The reaction was then stirred at room temperature overnight then partitioned between EtOAc (100 mL) and H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 30 mL). The combined organic layers were then washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to a thick oil. Purification by flash chromatography (25% EtOAc/hexane) afforded 830 mg (78%) of 3,4-dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one as a white solid. Data for 3,4-dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.90 (m, 3H), 6.67 (d, *J* = 7.7, 1H), 3.69 (bs, 1H), 3.36 (s, 3H), 1.37 (s, 6H).

3,4-Dihydro-1,3,3-trimethyl-6-nitroquinoxalin-2(1*H*)-one (Structure **45** of **Scheme X**, where $R^6 = R^7 = R^{13} = Me$). In a 50-mL r.b. flask, a solution of 3,4-dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one (830 mg, 4.36 mmol) in 20 mL of conc. H_2SO_4 was cooled to –15 °C. A solution of HNO_3 (336 mg, 4.80 mmol, 1.1 equiv) dissolved in conc. H_2SO_4 (1 mL) was then added dropwise via syringe in order to maintain a temperature below –5 °C. After complete addition the reaction was allowed to stir at –15 °C for 15 min, warmed to rt, poured over NaOH (15 g) pellets and ice. After complete solution of the NaOH pellets, the red precipitate was filtered, redissolved in EtOAc (150 mL), washed with H_2O (20 mL), brine (20 mL), dried ($MgSO_4$), filtered, and concentrated to give a orange solid. No further purification is required to obtain 960 mg (94%) of 3,4-dihydro-1,3,3-trimethyl-6-nitroquinoxalin-2(1*H*)-one as an orange solid. Data for 3,4-dihydro-1,3,3-trimethyl-6-nitroquinoxalin-2(1*H*)-one: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76 (dd, *J* = 8.8, 2.5, 1H), 7.55 (d, *J* = 2.4, 1H), 6.96 (d, *J* = 8.9, 1H), 4.04 (bs, 1H), 3.42 (s, 3H), 1.41 (s, 6H).

6-Amino-3,4-dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one (Structure **46** of **Scheme X**, where $R^6 = R^7 = R^{13} = Me$). In a Parr shaker apparatus, a solution 3,4-dihydro-1,3,3-trimethyl-6-nitroquinoxalin-2(1*H*)-one (960 mg, 4.08 mmol) in 50 mL of EtOAc:EtOH (1:1) and a catalytic amount of 10% Pd on activated carbon (96 mg, 10 wt-

%) were shaken under an atmosphere of hydrogen gas at 45 psi overnight. The reaction mixture was filtered through a pad of celite. The filtrate and EtOH washings were combined and concentrated to give 838 mg (100%) of 6-amino-3,4-dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one, purple brown solid. Data for 6-amino-3,4-dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.69 (d, *J* = 8.42, 1H), 6.19 (dd, *J* = 8.5, 2.4, 1H), 6.05 (d, *J* = 2.4, 1H), 3.55 (bs, 1H), 3.31 (s, 3H), 1.35 (s, 6H).

1,3,4,6-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-g]quinolin-2,7-dione (Compound **154**, Structure **47** of **Scheme X**, where R^1 = H, R^2 = trifluoromethyl, $R^6 = R^7 = R^{13}$ = Me). In a 100-mL r.b. flask, a solution of 6-amino-3,4-dihydro-1,3,3-trimethylquinoxalin-2(1*H*)-one (500 mg, 2.44 mmol) and ethyl-4,4,4-trifluoroacetoacetate (0.46 mL, 3.16 mmol, 1.3 equiv) in toluene (40 mL) was heated to reflux with stirring overnight. Removal of solvent followed be treatment of the crude product with conc H_2SO_4 (10 mL) at 100 °C for 10 h, cooled to rt, poured onto ice and the pH adjusted to 7 with NaOH pellets. The aqueous phase was extracted with EtOAc (4 x 50 mL), combined, washed with brine, dried ($MgSO_4$), filtered, and concentrated to a brown oil. Purification by flash chromatography (EtOAc/hexane, 25% to 50%, gradient elution) afforded 80 mg (10%) of Compound **154** as a yellow solid. Data for Compound **154**: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 12.07 (s, 1H), 7.22 (s, 1H), 7.01 (s, 1H), 6.73 (s, 1H), 6.61 (s, 1H), 3.30 (s, 3H), 1.29 (s, 6H).

EXAMPLE 52

1,2,3,4-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-g]quinolin-7(6*H*)-one (Compound **155**, Structure **49** of **Scheme X**, where R^1 = H, R^2 = trifluoromethyl, $R^6 = R^7 = R^{13}$ = Me).

1,2,3,4-Tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-g]quinolin-2-one (Structure **48** of **Scheme X**, where R^1 = H, R^2 = trifluoromethyl, $R^6 = R^7 = R^{13}$ = Me). This compound was made according to General Method 12 (EXAMPLE 22) from Compound **154** (EXAMPLE 51) (40 mg, 0.12 mmol), cesium fluoride (28 mg, 0.18 mmol, 1.5 equiv), and 2-iodopropane (0.02 mL, 0.18 mmol, 1.5

equiv). The crude reaction mixture was purified by silica gel chromatography (EtOAc/hexane, 25% to 50% gradient elution) to afford 26 mg (56%) of 1,2,3,4-tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinolin-2-one as an off-white solid. Data for 1,2,3,4-tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinolin-2-one: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.06 (s, 1H), 6.96 (s, 1H), 5.49 (sep, J = 6.3, 1H), 4.17 (s, 1H), 3.47 (s, 3H), 1.45 (s, 6H), 1.39 (d, J = 6.3, 6H).

1,2,3,4-Tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinoline. This compound was made according to General Method 2 (EXAMPLE 1) from 1,2,3,4-tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinolin-2-one (25 mg, 0.07 mmol) and BH_3-DMS (0.14 mL, 0.27 mmol, 4.0 equiv). Purification by silica gel chromatography (EtOAc/hexane, 10% to 25% gradient) afforded 5 mg (25%) of 1,2,3,4-tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinoline as a pale yellow solid. Data for 1,2,3,4-tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.82 (s, 1H), 6.77 (s, 1H), 5.43 (sept, J = 6.1, 1H), 3.04 (s, 2H), 3.02 (s, 3H), 1.39 (d, J = 6.0, 6H),1.29 (s, 6H).

1,2,3,4-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinolin-7(6*H*)-one (Compound **155**, Structure **49 of Scheme X**, where R^1 = H, R^2 = trifluoromethyl, $R^6 = R^7 = R^{13}$ = Me). This compound was made according to General Method 15 (EXAMPLE 22) from 1,2,3,4-tetrahydro-7-isopropoxy-1,3,3-trimethyl-9-(trifluoromethyl)pyrazino[3,2-*g*]quinoline (5 mg, 0.02 mmol) to yield 2 mg (45%) of Compound **155**, a yellow solid. Data for Compound **155**: **^{1}H NMR** (400 MHz, DMSO-d_6) δ 11.75 (broad s, 1H), 6.97 (s, 1H), 6.39 (s, 1H), 6.37 (s, 1H), 5.23 (bs, 1H), 2.86 (s, 2H), 2.82 (s, 3H), 1.17 (s, 6H).

EXAMPLE 53

9-(Trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-g]quinolin-7-one (Compound **156**, Structure **54** of **Scheme XI**, where R^4 = H).

6-Bromo-7-chloro-2-isopropoxy-4-(trifluoromethyl)quinoline (Structure **51** of **Scheme XI**). This compound was prepared according to General Method 11 (EXAMPLE 22) from 4-bromo-3-chloroaniline (2.06 g, 10.0 mmol), ethyl 4,4,4-trifluoroacetoacetate (2.30 g, 12.5 mmol) in 50 mL toluene followed by heating in 33 mL conc. H_2SO_4 to afford 2.08 g (64%) of 6-bromo-7-chloro-4-(trifluoromethyl)-quinolin-2(1*H*)-one, an off-white solid. This material was converted to the corresponding imino ether according to General Method 12 (EXAMPLE 22) with isopropyl iodide (4.32 g, 25.4 mmol) and CsF (3.85 g, 25.4 mmol) in 32 mL DMF to afford 1.34 g (57%) of 6-bromo-7-chloro-2-isopropoxy-4-(trifluoromethyl)quinoline, a white solid, after flash chromatography (hexanes). Data for 6-bromo-7-chloro-2-isopropoxy-4-(trifluoromethyl)quinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.22 (broad s, 1H), 8.00 (s, 1H), 7.17 (s, 1H), 5.51 (hept, 1H, *J* = 6.2), 1.40 (d, 6H, *J* = 6.2).

2-{[6-Bromo-2-isopropoxy-4-(trifluoromethyl)-7-quinolinyl]sulfanyl}-1-ethanamine (Structure **52** of **XI**, where R^4 = H). A solution of 6-bromo-7-chloro-2-isopropoxy-4-(trifluoromethyl)quinoline (0.500 g, 1.36 mmol), 2-aminoethanethiol hydrochloride (0.185 g, 1.63 mmol), NaH (60% in mineral oil, 0.136 g, 3.40 mmol) in 6.8 mL DMF was stirred at 0 °C, then allowed to warm to rt. After 4h, the mixture was poured into a cold saturated NH_4Cl:water (60 mL, 1:1). The solution was extracted with EtOAc (2 x 60 mL), and the combined organic layers washed sequentially with water (30 mL), brine (30 mL), dried over MgSO4, filtered, and concentrated. Flash chromatography (9:1 CH_2Cl_2:MeOH) afforded 0.404 g (73%) of 2-{[6-bromo-2-isopropoxy-4-(trifluoromethyl)-7-quinolinyl]sulfanyl}-1-ethanamine, a yellow-brown solid. Data for 2-{[6-bromo-2-isopropoxy-4-(trifluoromethyl)-7-quinolinyl]sulfanyl}-1-ethanamine: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.13 (broad s, 1H), 7.63 (s, 1H), 7.10 (s, 1H), 5.54 (hept, 1H, *J* = 6.2); 3.17-3.25 (m, 2H), 3.08-3.15 (m, 2H), 1.41 (d, 6H, *J* = 6.2).

2,3-Dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline (Structure **53** of **Scheme XI**, where R^4 = H). A 10 mL Schlenk flask was charged with palladium acetate (10.7 mg, 0.0476 mmol), *R*-BINAP (32.6 mg, 0.0524 mmol) and sodium *t*-butoxide (0.137 g, 1.43 mmol). The flask was placed under vacuum, then bled with nitrogen. This process was repeated twice. The solids were dissolved in 3 mL toluene, and a solution of 2-{[6-bromo-2-isopropoxy-4-(trifluoromethyl)-7-quinolinyl]sulfanyl}-1-ethanamine (0.390 g, 0.953 mmol) in 3.3 mL toluene was added. The flask was heated to 100 °C for 4h, whereupon the reaction was quenched with sat'd NH_4Cl (30 mL) and water (30 mL). The mixture was extracted with EtOAc (2 x 60 mL), and the combined organic layers washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated. Flash chromatography (4:1 hexanes:EtOAc) afforded 0.242 g (77%) of 2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline, a yellow solid. Data for 2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-g]quinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (s, 1H), 6.99 (s, 1H), 6.90 (broad s, 1H), 5.44 (hept, 1H, *J* = 6.2), 4.35 (broad s, 1H), 3.64-3.70 (m, 2H), 3.11-3.16 (m, 2H), 1.37 (d, 6H, *J* = 6.2).

9-(Trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one (Compound **156**, Structure **54** of **Scheme XI**, where R^4 = H). This compound was prepared according to General Method 15 (EXAMPLE 22) from 2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline (15 mg, 0.046 mmol) and 0.15 mL conc. HCl and 0.5 mL HOAc to afford 12 mg (91%) of Compound **156**, a yellow solid. Data for Compound **156**: **^{1}H NMR** (400 MHz, ace-d_6) δ 10.8 (v broad s, 1H), 7.12 (s, 1H), 6.92 (broad s, 1H), 6.75 (s, 1H), 5.74 (broad s, 1H), 3.58-3.64 (m, 2H), 3.12-3.20 (m, 2H).

EXAMPLE 54

1-Methyl-9-(trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one (Compound **157**, Structure **56** of **Scheme XI**, where R^4 = H, R^x = Me).

2,3-Dihydro-1-methyl-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-g]quinoline (Structure **55** of **Scheme XI**, where R^4 = H, R^x = Me). To a solution of 2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-g]quinoline (11 mg,

0.033 mmol) and paraformaldehyde (9.9 mg, 0.33 mmol) in 0.5 mL acetic acid was added $NaBH_3CN$ (12 mg, 0.19 mmol). After 16 h, the solution was quenched with sat'd $NaHCO_3$ (20 mL), and was extracted with EtOAc (20 mL). The organic layer was washed sequentially with sat'd $NaHCO_3$ (10 mL) and brine (10 mL), dried over $MgSO_4$, filtered and concentrated to afford 11 mg (97%) of 2,3-dihydro-1-methyl-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline, a yellow solid. Data for 2,3-dihydro-1-methyl-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.01 (s, 1H), 6.98 (broad s, 1H), 5.45 (hept, 1H, *J* = 6.2), 3.58-3.64 (m, 2H), 3.14-3.20 (m, 2H), 3.05 (s, 3H), 1.37 (d, 6H, *J* = 6.2).

1-Methyl-9-(trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one (Compound **157**, Structure **56** of **Scheme XI**, where R^4 = H, R^x = H). This compound was prepared according to General Method 15 (EXAMPLE 22) from 2,3-dihydro-1-methyl-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline (11 mg, 0.032 mmol) and 0.2 mL HCl and 0.6 mL HOAc heated at 80 °C for 3 h to afford 7 mg (73%) of Compound **157**, a yellow solid, after flash chromatography (23:2 CH_2Cl_2:MeOH). Data for Compound **157**: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 11.5 (broad s, 1H), 7.11 (s, 1H), 6.95 (s, 1H), 6.90 (broad s, 1H), 3.52-3.60 (m, 2H), 3.15-3.20 (m, 2H), 3.01 (s, 3H).

EXAMPLE 55

1-(2,2,2-trifluoroethyl)- 9-(trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one (Compound **158**, Structure **56** of **Scheme XI**, where R^4 = H, R^x = CF_3).

2,3-Dihydro-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline (Structure **55** of **Scheme XI**, where R^4 = H, R^x = CF_3). This compound was prepared according to General Method 7 (EXAMPLE 5) from 2,3-dihydro-7-isopropoxy-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline (11 mg, 0.034 mmol), trifluoroacetaldehyde ethyl hemiacetal (49 mg, 0.34 mmol) and $NaBH_3CN$ (14 mg, 0.22 mmol) in 0.7 mL TFA to afford 7.8 mg (56%) of 2,3-dihydro-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline, a yellow oil, after flash chromatography (9:1 hexanes:EtOAc). Data for 2,3-dihydro-7-

isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.21 (broad s, 1H), 7.03 (s, 1H), 5.46 (hept, 1H, *J* = 6.1), 3.97 (q, 2H, *J* = 8.8), 3.77-3.83 (m, 2H), 3.08-3.14 (m, 2H), 1.38 (d, 6H, *J* = 6.1).

1-(2,2,2-Trifluoroethyl)- 9-(trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one (Compound **158**, Structure **56** of **Scheme XI**, where R^4 = H, R^x = CF_3). This compound was prepared according to General Method 15 (EXAMPLE 22) from 2,3-dihydro-7-isopropoxy-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]thiazino[3,2-*g*]quinoline (7.8 mg, 0.019 mmol) in 0.2 mL HCl and 0.6 mL HOAc to afford 3.6 mg (51%) of Compound **158**, a yellow solid, after flash chromatography (23:2 CH_2Cl_2:MeOH). Data for Compound **158**: **^{1}H NMR** (400 MHz, ace-d_6) δ 10.8 (broad s, 1H), 7.21 (s, 1H), 7.15 (broad s, 1H), 6.80 (s, 1H), 4.18 (q, 2H, *J* = 9.3), 3.77-3.83 (m, 2H), 3.18-3.24 (m, 2H).

EXAMPLE 56

Steroid Receptor Activity

Utilizing the "cis-trans" or "co-transfection" assay described by Evans et al., Science, 240:889-95 (May 13, 1988), the disclosure of which is herein incorporated by reference, the compounds of the present invention were tested and found to have strong, specific activity as both agonists, partial agonists and antagonists of AR. This assay is described in further detail in U.S. Patent Nos. 4,981,784 and 5,071,773, the disclosures of which are incorporated herein by reference.

The co-transfection assay provides a method for identifying functional agonists and partial agonists that mimic, or antagonists that inhibit, the effect of native hormones, and quantifying their activity for responsive IR proteins. In this regard, the co-transfection assay mimics an *in vivo* system in the laboratory. Importantly, activity in the co-transfection assay correlates very well with known *in vivo* activity, such that the co-transfection assay functions as a qualitative and quantitative predictor of a tested compounds *in vivo* pharmacology. See, e.g., T. Berger et al. 41 *J. Steroid Biochem. Molec. Biol.* 773 (1992), the disclosure of which is herein incorporated by reference.

In the co-transfection assay, a cloned cDNA for an IR (e.g., human PR, AR or GR) under the control of a constitutive promoter (e.g., the SV 40 promoter) is introduced by transfection (a procedure to induce cells to take up foreign genes) into a background cell substantially devoid of endogenous IRs. This introduced gene directs the recipient cells to make the IR protein of interest. A second gene is also introduced (co-transfected) into the same cells in conjunction with the IR gene. This second gene, comprising the cDNA for a reporter protein, such as firefly luciferase (LUC), controlled by an appropriate hormone responsive promoter containing a hormone response element (HRE). This reporter plasmid functions as a reporter for the transcription-modulating activity of the target IR. Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally expressed by a gene under control of the target receptor and its native hormone.

The co-transfection assay can detect small molecule agonists or antagonists of target IRs. Exposing the transfected cells to an agonist ligand compound increases reporter activity in the transfected cells. This activity can be conveniently measured, e.g., by increasing luciferase production, which reflects compound-dependent, IR-mediated increases in reporter transcription. To detect antagonists, the co-transfection assay is carried out in the presence of a constant concentration of an agonist to the target IR (e.g., progesterone for PR) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (e.g., luciferase production). The co-transfection assay is therefore useful to detect both agonists and antagonists of specific IRs. Furthermore, it determines not only whether a compound interacts with a particular IR, but whether this interaction mimics (agonizes) or blocks (antagonizes) the effects of the native regulatory molecules on target gene expression, as well as the specificity and strength of this interaction.

The activity of selected steroid receptor modulator compounds of the present invention were evaluated utilizing the co-transfection assay, and in standard IR binding assays, according to the following illustrative Examples.

Co-transfection assay

CV-1 cells (African green monkey kidney fibroblasts) were cultured in the presence of Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10%

charcoal resin-stripped fetal bovine serum (CH-FBS) then transferred to 96-well microtiter plates one day prior to transfection.

To determine AR agonist and antagonist activity of the compounds of the present invention, the CV-1 cells were transiently transfected by calcium phosphate coprecipitation according to the procedure of Berger et al., 41 *J. Steroid Biochem. Mol. Biol.*, 733 (1992) with the following plasmids: pRShAR (5 ng/well), MTV-LUC reporter (100 ng/well), pRS-ß-Gal (50 ng/well) and filler DNA (pGEM; 45 ng/well). The receptor plasmid, pRShAR, contains the human AR under constitutive control of the SV-40 promoter, as more fully described in J.A. Simental et al., "Transcriptional activation and nuclear targeting signals of the human androgen receptor", 266 *J. Biol. Chem.*, 510 (1991).

The reporter plasmid, MTV-LUC, contains the cDNA for firefly luciferase (LUC) under control of the mouse mammary tumor virus (MTV) long terminal repeat, a conditional promoter containing an androgen response element. See e.g., Berger et al. supra. In addition, pRS-ß-Gal, coding for constitutive expression of E. coli ß-galactosidase (ß-Gal), was included as an internal control for evaluation of transfection efficiency and compound toxicity.

Six hours after transfection, media was removed and the cells were washed with phosphate-buffered saline (PBS). Media containing reference compounds (i.e. progesterone as a PR agonist, mifepristone ((11beta,17beta)-11-[4-(dimethylamino)phenyl]-17-hydroxy-17-(1-propynyl)estra-4,9-dien-3-one: RU486; Roussel Uclaf) as a PR antagonist; dihydrotestosterone (DHT; Sigma Chemical) as an AR agonist and 2-OH-flutamide (the active metabolite of 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl]pronanamide; Schering-Plough) as an AR antagonist; estradiol (Sigma) as an ER agonist and ICI 164,384 (N-butyl-3,17-dihydroxy-N-methyl-(7-alpha,17-beta)-estra-1,3,5(10)-triene-7-undecanamide; ICI Americas) as an ER antagonist; dexamethasone (Sigma) as a GR agonist and RU486 as a GR antagonist; and aldosterone (Sigma) as a MR agonist and spironolactone ((7-alpha-[acetylthio]-17-alpha-hydroxy-3-oxopregn-4-ene-21-carboxylic acid gamma-lactone; Sigma) as an MR antagonist) and/or the modulator compounds of the present invention in concentrations ranging from 10^{-12} to 10^{-5} M were added to the cells. Three to four replicates were used

for each sample. Transfections and subsequent procedures were performed on a Biomek 1000 automated laboratory work station.

After 40 hours, the cells were washed with PBS, lysed with a Triton X-100-based buffer and assayed for LUC and ß-Gal activities using a luminometer or spectrophotometer, respectively. For each replicate, the normalized response (NR) was calculated as:

LUC response/ß-Gal rate

where ß-Gal rate = ß-Gal/ß-Gal incubation time.

The mean and standard error of the mean (SEM) of the NR were calculated. Data was plotted as the response of the compound compared to the reference compounds over the range of the dose-response curve. For agonist experiments, the effective concentration that produced 50% of the maximum response (EC_{50}) was quantified. Agonist efficacy was a function (%) of LUC expression relative to the maximum LUC production by the reference agonist for PR, AR, ER, GR or MR. Antagonist activity was determined by testing the amount of LUC expression in the presence of a fixed amount of DHT as an AR agonist and progesterone as a PR agonist at the EC_{50} concentration. The concentration of test compound that inhibited 50% of LUC expression induced by the reference agonist was quantified (IC_{50}). In addition, the efficacy of antagonists was determined as a function (%) of maximal inhibition.

Table 1: Agonist, partial agonist, antagonist and binding activity of androgen receptor modulator compounds of present invention and the reference agonist compound, dihydrotestosterone (**DHT**), and reference antagonists compound, 2-hydroxyflutamide (**Flut**) and Casodex (**Cas**), on hAR in CV-1 cells.

Cmpd	AR Agonist CV-1 Cells		AR Antagonist CV-1 Cells	
No.	Efficacy (%)	Potency (nM)	Efficacy (%)	Potency (nM)
101	56	18	na	na
102	na[1]	na	58	22
103	92	6.4	24	8000
104	na	na	68	26
105	88	3.5	na	na
106	80	4	na	na
107	92	26	na	na
108	80	14	na	na
109	na	na	57	24
110	90	44	na	na
111	88	2.4	na	na
112	80	2.6	na	na
113	na	na	78	61
114	94	6.2	na	na
115	82	7.8	na	na
116	24	39	35	14
117	36	40	na	na
118	76	11	na	na
119	20	39	na	na
120	na	na	69	112
121	69	1.4	na	na
122	na	na	75	632
123	91	3.4	na	na
124	54	3.6	na	na
125	74	0.70	na	na
128	na	na	42	1345
129	42	1340	76	13
130	48	8.9	na	na
131	46	31	na	na
132	72	1.7	na	na
137	na	na	84	18
145	69	6	30	5024
DHT	100	6	na	na
Fluox	120	2.8	na	na
Flut	na	na	83	25
Cas	na	na	81	201

1 na = not active (i.e. efficacy of <20 and potency of >10,000 nM for the cotransfection assay, and Ki > 1000 nM for the binding assay).

nt = not tested.

Table 2: Overall agonist and antagonist potency of selected androgen receptor modulator compounds of present invention and the reference agonist and antagonist compounds shown in Table 1 on PR, AR, ER, GR and MR.

Cmpd	PR Potency		AR Potency		ER Potency		GR Potency	MR Potency
No.	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Agon (nM)	Antag (nM)	Antag (nM)	Antag (nM)
101	na	na	18	na	na	na	6500	na
102	na	4100	na	22	na	5900	3200	na
103	na	4500	6.4	8000	na	na	na	na
104	na	2000	na	26	na	na	830	1800
105	na	3000	3.5	na	na	na	6700	na
114	na	na	6.2	na	na	na	na	na
121	na	415	1.4	na	na	na	1050	2570
123	na	2470	3.4	na	na	na	3160	na
137	na	na	na	18	na	na	na	na
Fluox	1210	224	2.8	na	na	na	263	193
Prog	4	na	1300	na	na	na	na	nt
RU486	na	0.1	na	12	na	1500	0.7	1100
DHT	na	1800	6	na	1700	na	na	nt
Flut	na	1900	na	26	na	na	na	na
Estr	nt	nt	na	na	7	na	na	nt
ICI 164	na	na	na	na	na	160	na	na
Spir	nt	268	nt	nt	na	na	2000	25

na = not active (i.e., efficacy of >20 and potency of >10,000); nt = not tested.

EXAMPLE -57

The activity of selected compounds of the present invention as AR agonists was investigated in an immature castrated male rat model, a recognized test of the androgen activity of a given compound, as described in L. G. Hershberger et al., "Myotrophic Activity of 19-Nortestosterone and Other Steroids Determined by Modified Levator Ani Muscle Method" 83 *Proc. Soc. Exptl. Biol. Med.*, 175 (1953), and P. C. Walsh and R. F.

Gittes, "Inhibition of extratesticular stimuli to prostatic growth in the castrated rat by antiandrogens", 86 *Endocrinology*, 624 (1970); the disclosures of which are herein incorporated by reference.

The basis of this assay is the fact that the male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone (DHT), within the prostate by 5-alpha-reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, and about 40% of that in 65-year-old men. F. Labrie et al. 16 *Clin. Invest. Med.*, 475–492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostatic tissue. M. C. Luke and D. S. Coffey, "The Physiology of Reproduction" ed. by E. Knobil and J. D. Neill, 1, 1435–1487 (1994). Since the male sex organs are the tissues most responsive to modulation of androgen activity, this model is used to determine the androgen-dependent growth of the sex accessory organs in immature castrated rats. In addition to the prostate and seminal vesicles, the levator ani demonstrates androgen dependent growth (Herschberger, *supra*). Androgens which show the greatest levator ani growth also show the greatest anabolic activity by nitrogen retention methods. Hence, the levator ani is a useful endpoint to measure myotrophic effects on muscle. Compounds which show anabolic activities could be useful in the treatment of muscle-wasting disorders. Further, compounds which possess such anabolic activity without concomitant androgenic activity (tissue selectivity) would be of practical therapeutic value. Male immature rats (50–60 g, 21-day-old, Sprague-Dawley, Harlan) were castrated under metofane anesthesia. Immediately after surgery, animals groups were dosed for 3 days as follows:

(1) control vehicle;

(2) Fluoxymesterone (Fluox) (1.0, 3.0, and 100 mg/kg, oral administration daily); and

(3) a compound of the present invention (different doses, oral administration daily) to demonstrate agonist activity

At the end of the 3-day treatment, the animals were sacrificed, and the ventral prostates (VP), seminal vesicles (SV), and levator ani (LA) were collected and weighed. The sexual organ weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by the compounds of the present invention was compared to the castrate control animals. The organ weight of the intact control animals is considered fully efficacious (100%). Super-anova (one factor) was used for statistical analysis.

The gain and loss of sexual organ weights reflect the changes of cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., 145 *J Urol.*, 188–191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weights is sufficient to indicate the bioactivity of androgens and androgen antagonists. In immature castrated rats, replacement of exogenous androgens increased the weights of the ventral prostate (VP), the seminal vesicles (SV), and the levator ani (LA) in a dose-dependent manner as shown in Table 4.

Table 4: Androgen Induced Ventral Prostate, Seminal Vesicle, and Levator Ani Growth in castrated immature rats at oral dosing, once daily, for 3 days, with fluoxymesterone (fluox) and Compound **105**.

Treatment (mg/kg)	VP (wet wt)[1]	VP eff (% of intact)[2]	SV (wet wt)[1]	SV eff (% intact)[2]	LA (wet wt)[1]	LA eff (% intact)[2]
Cx	24.2 ± 1.8	0.0 ± 8.1	7.7 ± 1.0	0.0 ± 20	27.7 ± 3.2	0.0 ± 163
intact	46.6 ± 3.4	100 ± 15	12.8 ± 1.3	100 ± 25	29.5 ± 1.0	100 ± 60
105 (3)	26.9 ± 1.1	12 ± 5	8.5 ± 0.7	15 ± 13	33.0 ± 2.4	306 ± 140
105 (10)	35.9 ± 2.7	52 ± 12	9.9 ± 0.4	42 ± 8.2	36.3 ± 1.3	498 ± 73
105 (30)	30.1 ± 2.1	26 ± 9	11.7 ± 1.4	78 ± 26	35.8 ± 1.2	469 ± 71
105 (100)	42.1 ± 1.6	80 ± 7	14.4 ± 1.0	131 ±19	39.7 ± 0.6	696 ± 36
Fluox (1)	49.3 ± 4.1	112 ± 18	24.3 ± 3.7	325 ± 73	44.6 ± 4.0	977 ± 230
Fluox (3)	57.5 ± 2.4	148 ± 10	31.8 ± 4.2	472 ± 82	45.3 ± 3.1	1020 ± 180
Fluox (100)	82.3 ± 7.2	259 ± 32	46.7 ± 1.7	762 ± 34	49.8 ± 5.4	1280 ± 310

[1] **Weight of organ in mg/100 g body weight.**

[2] **% Efficacy compared to intact control (100% is full maintenance).**

Table 5: Androgen Induced Ventral Prostate, Seminal Vesicle, and Levator Ani Growth in castrated immature rats at oral dosing, once daily, for 3 days, with fluoxymesterone (fluox) and Compound **123**.

Treatment (mg/kg)	VP (wet wt)[1]	VP eff (% of intact)[2]	SV (wet wt)[1]	SV eff (% of intact)[1]	LA (wet wt)[1]	LA eff (% of intact)[2]
Cx	26.6 ± 2.1	0.0 ± 12	9.4 ± 0.8	0.0 ± 11	30.0 ± 3.6	0.0 ± 163
intact	44.0 ± 5.1	100 ± 29	17 ± 1.5	100 ± 19	32.1 ± 3.0	100 ± 137
123 (3)	28.8 ± 2.8	13 ± 16	10.6 ± 0.9	15 ± 12	32.4 ± 3.6	109 ± 165
123 (10)	38.6 ± 0.6	69 ± 3.6	9.3 ± 0.3	-1 ± 4.2	34.4 ± 1.6	203 ± 75
123 (30)	37.9 ± 3.1	65 ± 18	13.9 ± 0.8	57 ± 9.9	42.1 ± 2.7	554 ± 124
123 (100)	44.6 ± 5.3	101 ± 30	19.6 ± 1.5	129 ± 19	48.5 ± 2.0	844 ± 91
Fluox (1)	31.8 ± 3.8	30 ± 22	22.4 ± 3.2	165 ± 41	42.6 ± 2.6	574 ± 116
Fluox (3)	47.1 ± 3.4	118 ± 19	29.0 ± 2.0	250 ± 26	51.8 ± 1.4	995 ± 65
Fluox (100)	73.5 ± 3.5	269 ± 20	37.4 ± 1.1	356 ± 14	60.4 ± 1.1	1384 ± 51

[1] Weight of organ in mg/100 g body weight.

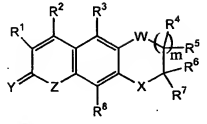
[2] % Efficacy compared to intact control (100% is full maintenance).

In this immature castrated rat model, a known AR agonist (fluoxymesterone) was administered orally with 1.0, 3.0, and 100 mg/kg, increasing the androgen-mediated increases in the weights of VP, SV and LA in a dose-dependent manner as shown in Table 4. Compounds **105** and **123** also exhibited AR agonist activity by promoting the androgen-mediated maintenance/increase in the weights of the VP, SV and LA as summarized in Tables 4 and **5**.

While in accordance with the patent statutes, description of the preferred embodiments and processing conditions have been provided, the scope of the invention is not to be limited thereto or thereby. Various modifications and alterations of the present invention will be apparent to those skilled in the art without departing from the scope and spirit of the present invention, reference is made to the following non-limiting enumerated embodiments.

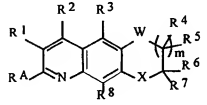
What is claimed is:

1. A compound of the formula:



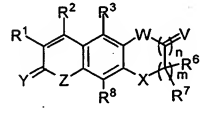
(I)

OR



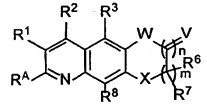
(II)

OR



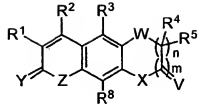
(III)

OR



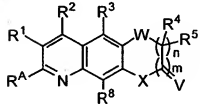
(IV)

OR



(V)

OR



(VI)

wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_mR^9$, $C_1 - C_8$ alkyl, $C_1 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, $C_1 - C_8$ aryl, $C_1 - C_8$ arylalkyl, $C_1 - C_8$ heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2Cl, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^3 is selected from the group of hydrogen, F, Cl, Br, I, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, or $C_1 - C_6$ alkyl, $C_1 - C_6$ heteroalkyl and $C_1 - C_6$ haloalkyl and wherein the alkyl, heteroalkyl and haloalkyl groups are optionally substituted;

R^4 and R^5 are each independently selected from the group of hydrogen, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 -$

C_8 heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted, or

R^4 and R^5 taken together form a saturated or unsaturated three- to seven-membered ring that is optionally substituted;

R^6 and R^7 are each independently selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted, or

R^6 and R^7 taken together form a saturated or unsaturated three- to seven-membered ring that is optionally substituted, or

R^6 and R^5 taken together form a saturated or unsaturated three- to seven-membered ring that is optionally substituted;

R^8 is selected from the group of hydrogen, C_1 - C_4 alkyl, $C_1 - C_4$ heteroalkyl, $C_1 - C_4$ haloalkyl, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$ and $S(O)_mR^9$ and wherein the alkyl, heteroalkyl and haloalkyl groups are optionally substituted;

R^9 is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, arylalkyl, C_2-C_4 alkynyl and C_2-C_8 alkenyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^{10} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, $C(Y)R^{12}$, $C(Y)OR^{12}$, aryl, heteroaryl, C_2-C_4 alkynyl, C_2-C_8 alkenyl, arylalkyl, SO_2R^{12} and $S(O)R^{12}$ and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^{11} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, arylalkyl, C_2-C_4 alkynyl and C_2-C_8 alkenyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^{12} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, arylalkyl, C_2-C_4 alkynyl and C_2-C_8 alkenyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted,

R^{13} is selected from the group of hydrogen, C_1 – C_8 alkyl, C_3 – C_8 cycloalkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, C_2-C_4 alkynyl and C_2-C_8 alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkynyl, and alkenyl groups are optionally substituted; or

R^{13} and R^4 taken together form a saturated or unsaturated three- to seven-membered ring that is optionally substituted; or

any two of R^4 through R^7, and R^{13} taken together form a saturated or unsaturated three- to seven-membered ring that is optionally substituted;

R^{14} and R^{15} are each independently selected from the group of hydrogen, C_1 – C_8 alkyl, C_3 – C_8 cycloalkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, aryl, heteroaryl, arylalkyl, C_2 – C_8 alkynyl and C_2 – C_8 alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, arylalkyl, alkynyl and alkenyl are optionally substituted;

R^A is selected from the group of hydrogen, F, Br, Cl, I, CN, C_1 – C_6 alkyl, C_1 – C_6 haloalkyl, C_1 – C_6 heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{17}R^{17}$, SOR^{17} and SO_2R^{17} and wherein the alkyl, haloalkyl and heteroalkyl groups are optionally substituted;

R^{16} is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, C_1-C_8 heteroalkyl, COR^{17}, CO_2R^{17}, $CONR^{17}R^{17}$, C_2-C_8 alkynyl, C_2-C_8 alkenyl, aryl, and heteroaryl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^{17} is selected from the group of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl and wherein the alkyl, haloalkyl, and heteroalkyl groups are optionally substituted;

m is 0, 1 or 2;

n is 1 or 2;

V is selected from the group of O, S and $CR^{14}R^{15}$;

W is selected from the group of O, S, NH, NR^{13}, $NC(Y)R^{11}$ and NSO_2R^{11};

X and Z each independently is selected from the group of O, $S(O)_m$, NH, NR^{11}, $NC(Y)R^{11}$, NSO_2R^{12} and $NS(O)R^{12}$; and

Y is O or S;

and pharmaceutically acceptable salts thereof.

2. A compound according to claim 1, wherein Z is NR^{11}.

3. A compound according to claim 2, wherein R^{11} is hydrogen.

4. A compound according to claim 2, wherein R^2 is CF_3.

5. A compound according to claim 1, wherein W is NR^{13}.

6. A compound according to claim 5, wherein R^{13} and one of R^4 and R^5 together form a five or six-membered ring.

7. A compound according to claim 5, wherein R^{13} is alkyl.

8. A compound according to claim 7, wherein R^{13} is selected from the group of methyl, ethyl, propyl, isopropyl, cyclopropylmethyl, and t-butyl.

9. A compound according to claim 5, wherein R^{13} is haloalkyl.

10. A compound according to claim 9, wherein R^{13} is trifluoroethyl.

11. A compound according to claim 1, wherein each of R^4, R^5, R^6 and R^7 are independently hydrogen or optionally substituted C_1-C_6 alkyl.

12. A compound according to claim 11, wherein one of R^4, R^5, R^6 and R^7 is optionally substituted C_1-C_6 alkyl.

13. A compound according to claim 11, wherein one of R^4 and R^5 is optionally substituted C_1-C_6 alkyl.

14. A compound according to claim 13, wherein one of R^4 and R^5 is OR^9.

15. A compound according to any one of claims 11 or 13, wherein one of R^6 and R^7 is optionally substituted C_1-C_6 alkyl.

16. A compound according to claim 15, wherein one of R^6 and R^7 is OR^9.

17. A compound according to claim 1, wherein R^3 and R^8 are each hydrogen; X and Y are each independently O or S; W is NR^{13}; and Z is NR^{11}.

18. A compound according to claim 17, wherein X and Y are each O.

19. A compound according to claim 18, wherein R^2 is selected from the group of hydrogen, halogen, CF_3, $C_1 - C_8$ alkyl and $C_1 - C_8$ haloalkyl.

20. A compound according to claim 19, wherein R^2 is CF_3.

21. A compound according to claim 20, wherein R^{13} is selected from the group of $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, and $C_1 - C_8$ haloalkyl.

22. A compound according to claim 21, wherein R^{13} is $C_1 - C_8$ alkyl or $C_1 - C_8$ haloalkyl.

23. A compound according to claim 21, wherein R^{11} is selected from the group of hydrogen, optionally substituted $C_1 - C_6$ alkyl and $C_1 - C_6$ heteroalkyl.

24. A compound according to claim 23, wherein R^{11} is hydrogen or optionally substituted $C_1 - C_6$ alkyl.

25. A compound according to claim 24, wherein R^{11} is hydrogen.

26. A compound according to claim 23, wherein R^6 and R^7 are each independently selected from the group of hydrogen , $C_1 - C_8$ alkyl, and $C_1 - C_8$ haloalkyl.

27. A compound according to claim 26, wherein R^6 and R^7 are each independently hydrogen or $C_1 - C_8$ alkyl.

28. A compound according to claim 27, wherein R^6 and R^7 are each hydrogen.

29. A compound according to claim 26, wherein R^4 and R^5 are each independently selected from the group of hydrogen, $C_1 - C_8$ alkyl, and OR^9.

30. A compound according to claim 29, wherein R^4 and R^5 are each independently hydrogen or $C_1 - C_8$ alkyl.

31. A compound according to claim 30, wherein R^4 and R^5 are each hydrogen.

32. A compound according to claim 1, wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_6$ alkyl and $C_1 - C_6$ haloalkyl;

R^2 is selected from the group of hydrogen, halogen, CF_3, $C_1 - C_8$ alkyl, and $C_1 - C_8$ haloalkyl;

R^3 is selected from the group of hydrogen, $C_1 - C_8$ alkyl, and $C_1 - C_8$ haloalkyl;

R^4 and R^5 are each independently selected from the group of hydrogen , $C_1 - C_8$ alkyl, C_1-C_4 haloalkyl, C_1-C_4 heteroalkyl and OR^9;

R^6 and R^7 are each independently hydrogen or $C_1 - C_8$ alkyl;

R^8 is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_4$ alkyl and $C_1 - C_4$ haloalkyl;

R^A is selected from the group of hydrogen, F, Cl, Br, I, $C_1 - C_6$ alkyl and $C_1 - C_6$ haloalkyl;

m is 1 or 2;

W is selected from the group of O, NH, NR^{13}, $NC(Y)R^{11}$, and NSO_2R^{11};

X and Z are each independently selected from the group of O, S and NR^{11}; and

Y is O.

33. A compound according to claim 32, wherein:

R^1, R^3 and R^8 are each hydrogen;

R^2 is CF_3 or haloalkyl;

R^5, R^6, and R^7 each are independently hydrogen or $C_1 - C_8$ alkyl;

m is 1;

W is NH or NR^{13};

X and Z are each independently O or NR^{11}; and

Y is O.

34. A compound according to claim 33, wherein:

R^2 is CF_3;

R^4 is selected from the group of hydrogen, C_1-C_4 alkyl, and C_1-C_2 haloalkyl;

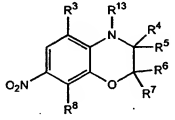
R^5, R^6, and R^7 are each independently hydrogen;

W is NR^{13};

X is O; and

Z is NR^{11}.

35. A method for the preparation of compounds of the formula:



wherein:

R^3 is selected from the group of hydrogen, F, Cl, Br, I, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, or $C_1 - C_6$ alkyl, $C_1 - C_6$ heteroalkyl and $C_1 - C_6$ haloalkyl and wherein the alkyl, heteroalkyl and haloalkyl groups are optionally substituted;

R^4 and R^5 are each independently selected from the group of hydrogen, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl are optionally substituted, or

R^4 and R^5 taken together can form a three- to seven-membered ring that is optionally substituted;

R^6 and R^7 are each independently selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl are optionally substituted, or

R^6 and R^7 taken together can form a three- to seven-membered ring that is optionally substituted; or

R^6 and R^5 taken together form a three- to seven-membered ring that optionally substituted; or

any two of R^4 through R^7 taken together form a three- to seven-membered ring that is optionally substituted;

R^8 is selected from the group of hydrogen, $C_1 - C_6$ alkyl, $C_1 - C_6$ heteroalkyl, $C_1 - C_6$ haloalkyl, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$ and $S(O)_mR^9$ and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^9 is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, $C_3 - C_6$ alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups are optionally substituted;

R^{10} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl, arylalkyl, SO_2R^{12} and $S(O)R^{12}$ and wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups are optionally substituted;

R^{11} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups are optionally substituted;

R^{12} is hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl or arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups are optionally substituted;

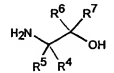
R^{13} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, heteroaryl, $C_3 - C_8$ alkenyl, arylalkyl and

heteroarylalkyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, heteroaryl, alkenyl and arylalkyl groups are optionally substituted;

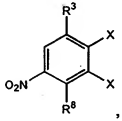
m is 0, 1, or 2;

that comprises the steps of:

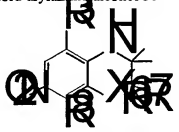
(a) treating either a single enantiomer, diastereomers, or the racemate of a β-aminoalcohol of the formula:



with a 3,4-dihalonitrobenzene of the formula:

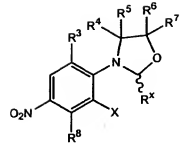


where X is fluorine or chlorine, to afford arylamino alcohol **36**



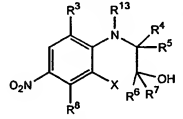
(36);

(b) treating arylamino alcohol **36** with aldehyde $R^x(CO)H$ or the corresponding hydrate or hemiacetal $R^x HC(OH)(OR)$, where R is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_1-C_{10} haloalkyl, and $R^x CH_2$ is equivalent to R^{13}, to form oxazolidine **37**



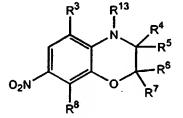
(37);

(c) reducing oxazolidine **37** to form amino alcohol **38**



(38); and

(d) treating amino alcohol **38** with a base to form the 3,4-dihydro-7-nitro-2H-1,4-benzoxazine intermediate **39**



(39)

as either a single enantiomer, diastereomers or the racemate.

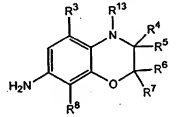
36. A method according to claim 35, wherein R^3, R^4, R^5, R^6, R^7, R^8 and R^{13} each independently are selected from the group of hydrogen, C_1-C_6 alkyl and C_1-C_6 haloalkyl.

37. A method according to claim 36, wherein R^3, R^6, R^7, and R^8 each are hydrogen.

38. A method according to claim 37, wherein one of R^4 and R^5 is hydrogen and the other one of R^4 and R^5 is C_1-C_6 alkyl or C_1-C_6 haloalkyl.

39. A method according to claim 38, wherein R^{13} is C_1-C_6 alkyl or C_1-C_6 haloalkyl.

40. A method for the preparation of compounds of the formula:



wherein:

R^3 is selected from the group of hydrogen, F, Cl, Br, I, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, or $C_1 - C_6$ alkyl, $C_1 - C_6$ heteroalkyl and $C_1 - C_6$ haloalkyl and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^4 and R^5 are each independently selected from the group of hydrogen, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted, or

R^4 and R^5 taken together can form a three- to seven-membered ring that is optionally substituted;

R^6 and R^7 are each independently selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted, or

R^6 and R^7 taken together form a three- to seven-membered ring that is optionally substituted; or

any two of R^4 through R^7 taken together can form a three- to seven-membered ring that is optionally substituted; or

R^6 and R^5 taken together form a three- to seven-membered ring that is optionally substituted;

R^8 is selected from the group of hydrogen, C_1 - C_4 alkyl, C_1 – C_4 heteroalkyl, C_1 – C_4 haloalkyl, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$ and $S(O)_mR^9$ and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^9 is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{10} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl, arylalkyl, SO_2R^{12} and $S(O)R^{12}$ and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{11} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

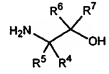
R^{12} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 allyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{13} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, heteroaryl, $C_3 - C_8$ alkenyl, arylalkyl and heteroarylalkyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

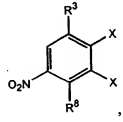
m is 0, 1, or 2;

that comprises the steps of:

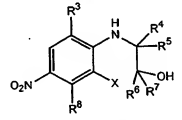
(a) treating either a single enantiomer, diastereomers, or the racemate of a β-aminoalcohol of the formula:



with a 3,4-dihalonitrobenzene of the formula:

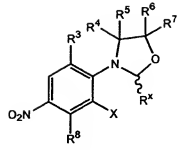


where X is fluorine or chlorine, to afford arylamino alcohol **36**



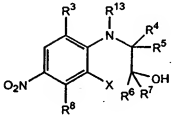
(36);

(b) treating arylamino alcohol **36** with aldehyde $R^x(CO)H$ or the corresponding hydrate or hemiacetal $R^x HC(OH)(OR)$, where R is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_1-C_{10} haloalkyl, and $R^x CH_2$ is equivalent to R^{13}, to form oxazolidine **37**



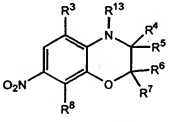
(37);

(c) reducing oxazolidine **37** to form amino alcohol **38**



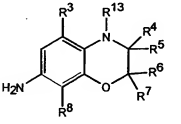
(38);

(d) treating amino alcohol **38** with a base to form the 3,4-dihydro-7-nitro-2H-1,4-benzoxazine compound **39**



(39); and

(e) treating nitro benzoxazine compound **39** with a reducing agent to form amino benzoxazine compound **40**:



(40).

41. A method according to claim 40, wherein R^3, R^4, R^5, R^6, R^7, R^8 and R^{13} are each independently selected from the group of hydrogen, C_1-C_6 alkyl or C_1-C_6 haloalkyl.

42. A method according to claim 41, wherein R^3, R^6, R^7, and R^8 each are hydrogen.

43. A method according to claim 42, wherein one of R^4 and R^5 is hydrogen and the other one of R^4 and R^5 is C_1-C_6 alkyl or C_1-C_6 haloalkyl.

44. A method according to claim 43, wherein R^{13} is C_1-C_6 alkyl or C_1-C_6 haloalkyl.

45. A compound according to claim 1, wherein said compound is selected from the group of:

1,2,3,6-Tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2,3,6-Tetrahydro-1,6-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1-Ethyl-1,2,3,6-tetrahydro-6-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

8-Fluoro-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

8-Chloro-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

9-(Difluoromethyl)-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2,3,6-Tetrahydro-6-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

7-Chloro-2,3-dihydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-1*H*-[1,4]oxazino[3,2-*g*]quinoline,

1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-*g*]quinolin-7-thione,

1,2,3,6-Tetrahydro-1-propyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2,3,6-Tetrahydro-1-isobutyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2,3,6-Tetrahydro-1-isobutyl-6-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(-)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-1,3-dimethyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-3-Ethyl-1,2,3,6-tetrahydro-1-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1-Cyclopropylmethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2,3,6-Tetrahydro-1-(pyridylmethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(+)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(-)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-trans-1,2,3,6-Tetrahydro-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-cis-1,2,3,6-Tetrahydro-2,3-dimethyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-trans-3-Ethyl-1,2,3,6-tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-cis-3-Ethyl-1,2,3,6-tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-2-(hydroxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-2-(acetoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(+)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(-)-1,2,3,6-Tetrahydro-2-(methoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-2-(Ethoxymethyl)-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-2-(propoxymethyl)-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2-Dihydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-3*H*-[1,4]oxazino[3,2-*g*]quinolin-2,7-dione,

(±)-1,2,3,6-Tetrahydro-2-hydroxy-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2-Dihydro-3-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-3*H*-[1,4]oxazino[3,2-*g*]-quinolin-2,7-dione

1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-2-thioxo-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1-Cyclopropylmethyl-1,2,3,6-tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-2-Ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1-Cyclopropylmethyl-2-ethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

1,2,3,6-Tetrahydro-1-isopropyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2-Diethyl-1,2,3,6-tetrahydro-9-(trifluoromethyl)-7H-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(+)-1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(-)-1,2,3,6-Tetrahydro-1-(2,2,2-trifluoroethyl)-2,9-bis(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1-Ethyl-1,2,3,6-tetrahydro-2-methyl-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(2R)-(-)-1,2,3,6-Tetrahydro-2-methyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(2*R*)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(2*R*)-2-Ethyl-1,2,3,6-tetrahydro-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(2*R*)-1,2,3,6-Tetrahydro-2-isopropyl-1-(2,2,2-trifluoroethyl)-9-(trifluoromethyl)-7*H*-[1,4]oxazino[3,2-*g*]quinolin-7-one,

(±)-1,2,3,4,4a,5-Hexahydro-11-(trifluoromethyl)-pyrido[1',2':4,5][1,4]oxazino[3,2-*g*]quinolin-7-one,

(*R*)-2,3,3a,4-Tetrahydro-10-(trifluoromethyl)-pyrrolo[1',2':4,5][1,4]oxazino[3,2-g]quinolin-8(7*H*)-one,

1,3,4,6-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)-pyrazino[3,2-g]quinolin-2,7-dione,

1,2,3,4-Tetrahydro-1,3,3-trimethyl-9-(trifluoromethyl)-pyrazino[3,2-g]quinolin-7(6*H*)one,

9-(Trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one,

1-Methyl-9-(trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one,

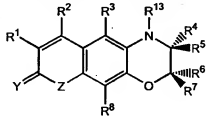
1-(2,2,2-Trifluoroethyl)-9-(trifluoromethyl)-1,2,3,6-tetrahydro-7*H*-[1,4]thiazino[3,2-*g*]quinolin-7-one.

46. A pharmaceutical composition comprising in a pharmaceutically acceptable vehicle suitable for enteral, parenteral, or topical administration, one or more compounds according to any one of claims 1, 20, 23, 26 and 29.

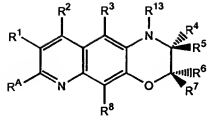
47. A compound according to any one of claims 1, 20, 23, 26 and 29 for administration to a mammalian subject to modulate a process mediated by one or more steroid receptors from the group consisting of progesterone receptors, androgen receptors, estrogen receptors, glucorticoid receptors, and mineralocorticoid receptors.

48. A compound according to any one of claims 1, 20, 23, 26 and 29 for use in modulation of male and female hormone responsive diseases.

49. A method for the preparation of compounds of the formula:



OR



wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_mR^9$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^3 is selected from the group of hydrogen, F, Cl, Br, I, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, or $C_1 - C_6$ alkyl, $C_1 - C_6$ heteroalkyl and $C_1 - C_6$ haloalkyl and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^4 and R^5 are each independently is selected from the group of hydrogen, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted, or

R^4 and R^5 taken together a three- to seven-membered ring that is optionally substituted;

R^6 and R^7 are each independently is selected from the group of hydrogen, C_1 – C_8 alkyl, C_3 – C_8 cycloalkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, aryl, arylalkyl, heteroaryl, C_2 – C_8 alkynyl, and C_2 – C_8 alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted; or

R^6 and R^7 taken together form a three- to seven-membered ring that is optionally substituted; or

any two of R^4 through R^7 taken together can form a three- to seven-membered ring that is optionally substituted; or

R^6 and R^5 taken together form a three- to seven-membered ring that is optionally substituted;

R^8 is selected from the group of hydrogen, C_1 - C_4 alkyl, C_1 – C_4 heteroalkyl, C_1 – C_4 haloalkyl, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$ and $S(O)_mR^9$ and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^9 is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{10} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl, arylalkyl, SO_2R^{12} and $S(O)R^{12}$ and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{11} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{12} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{13} is selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, heteroaryl, $C_3 - C_8$ alkenyl, arylalkyl and heteroarylalkyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^A is hydrogen, F, Br, Cl, I, CN, a $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{17}R^{17}$, SOR^{17} or SO_2R^{17} and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^{16} is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl., C_1-C_8 heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{17}R^{17}$ and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^{17} is selected from the group of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

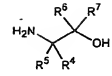
m is 0, 1, or 2;

Y is O or S;

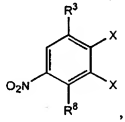
Z is selected from the group of O, $S(O)_m$, NH, NR^{11}, $NC(Y)R^{11}$, NSO_2R^{12} and $NS(O)R^{12}$;

that comprises the steps of:

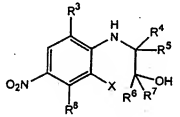
(a) treating either a single enantiomer, diastereomers, or the racemate of a β-aminoalcohol of the formula:



with a 3,4-dihalonitrobenzene of the formula

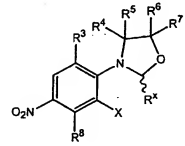


where X is fluorine or chlorine, to afford arylamino alcohol **36**



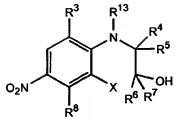
(36);

(b) treating arylamino alcohol **36** with aldehyde $R^x(CO)H$ or the corresponding hydrate or hemiacetal $R^x HC(OH)(OR)$, where R is H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_1-C_{10} haloalkyl, and R^x CH_2 is equivalent to R^{13}, to form oxazolidine **37**



(37)

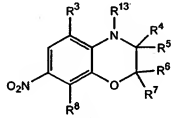
(c) reducing oxazolidine **37** to form amino alcohol **38**



(38);

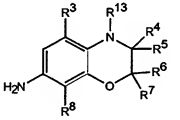
and

(d) treating amino alcohol **38** with a base to form the 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine intermediate **39**



(39);

(e) treating nitro benzoxazine compound **39** with a reducing agent to form amino benzoxazine compound **40**

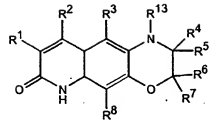


(40)

as either a single enantiomer, diastereomers, or the racemate; and

(f) treating amino benzoxazine compound **40** with a β–ketoester or its corresponding hydrate at elevated temperature to form acetanilide compound; and

(g) treating said acetanilide compound with an acid to yield quinoline compound **41**:

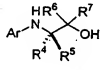


50. A method according to claim 49, wherein R^3, R^4, R^5, R^6, R^7, R^8 and R^{13} are each independently selected from the group of hydrogen, C_1-C_6 alkyl or C_1-C_6 haloalkyl.

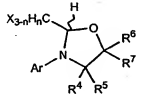
51. A method according to claim 49, wherein R^3, R^4, R^5, R^6, R^7, and R^8 are each hydrogen.

52. A method for the preparation of *N*-(2-haloethyl) arylamino alcohols comprising:

(a) treating either a single enantiomer, diastereomers, or the racemate of an arylamino alcohol of the formula

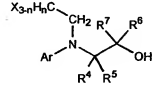


with aldehyde $CH_nX_{3-n}COH$ or the hydrate or hemiacetal $CH_nX_{3-n}CH(OH)OR$, where X is a halogen, n is 0, 1 or 2, and R is selected from the group of H, C_1-C_{10} alkyl, C_2-C_{10} alkenyl or C_1-C_{10} haloalkyl, in the presence of an acid catalyst to form an oxazolidine of the formula:



; and

(b) treating said oxazolidine with a reducing agent, preferably triethylsilane or sodium cyanoborohydride, in the presence of a Lewis acid or a Bronsted acid as a catalyst to form a product of the formula:

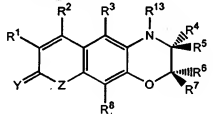


wherein

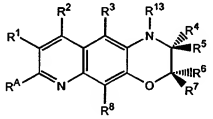
R^{4-7} are each independently selected from the group of hydrogen $C_1 - C_8$ alkyl, cycloalkyl, heteroalkyl, haloalkyl, allyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl, and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, allyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl are optionally substituted; and

Ar is aryl or heteroaryl, optionally substituted at one or more positions; as either a single enantiomer, diastereomers, or the racemate.

53. A method for the preparation of compounds of the formula



OR



wherein:

R^1 is selected from the group of hydrogen, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$, $S(O)_mR^9$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, or $C_2 - C_8$ alkenyl and wherein the alkyl,

cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally;

R^2 is selected from the group of hydrogen, F, Cl, Br, I, CF_3, CF_2H, CFH_2, CF_2OR^9, CH_2OR^9, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl groups are optionally substituted;

R^3 is selected from the group of hydrogen, F, Cl, Br, I, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C_1 - C_6$ alkyl, $C_1 - C_6$ heteroalkyl and $C_1 - C_6$ haloalkyl ;

R^4 and R^5 are each independently selected from the group of hydrogen, OR^9, $S(O)_mR^9$, $NR^{10}R^{11}$, $C(Y)OR^{11}$, $C(Y)NR^{10}R^{11}$, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl are optionally substituted, or

R^4 and R^5 taken together form a three- to seven-membered ring that is optionally substituted;

R^6 and R^7 are each independently selected from the group of hydrogen, $C_1 - C_8$ alkyl, $C_3 - C_8$ cycloalkyl, $C_1 - C_8$ heteroalkyl, $C_1 - C_8$ haloalkyl, aryl, arylalkyl, heteroaryl, $C_2 - C_8$ alkynyl, and $C_2 - C_8$ alkenyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, alkynyl, and alkenyl are optionally substituted; or

R^6 and R^7 taken together form a three- to seven-membered ring that is optionally substituted; or

any two of R^4 through R^7 taken together can form a three- to seven-membered ring that is optionally substituted;

R^6 and R^5 taken together form a three- to seven-membered ring that is optionally substituted;

R^8 is selected from the group of hydrogen, C_1 - C_4 alkyl, C_1 – C_4 heteroalkyl, C_1 – C_4 haloalkyl, F, Cl, Br, I, NO_2, OR^9, $NR^{10}R^{11}$ and $S(O)_mR^9$ and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^9 is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{10} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl, arylalkyl, SO_2R^{12} and $S(O)R^{12}$ and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{11} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{12} is selected from the group of hydrogen, C_1 - C_6 alkyl, C_1 - C_6 heteroalkyl, C_1 - C_6 haloalkyl, aryl, heteroaryl, C_3 - C_6 alkenyl and arylalkyl and wherein the alkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, and alkenyl groups are optionally substituted;

R^{13} is selected from the group of hydrogen, C_1 – C_8 alkyl, C_3 – C_8 cycloalkyl, C_1 – C_8 heteroalkyl, C_1 – C_8 haloalkyl, aryl, heteroaryl, C_3 – C_8 alkenyl, arylalkyl and heteroarylalkyl and wherein the alkyl, cycloalkyl, heteroalkyl, haloalkyl, aryl, arylalkyl, heteroaryl, arylalkyl and alkenyl groups are optionally substituted;

R^A is selected from the group of hydrogen, F, Br, Cl, I, CN, a $C_1 - C_6$ alkyl, $C_1 - C_6$ haloalkyl, $C_1 - C_6$ heteroalkyl, OR^{16}, $NR^{16}R^{17}$, SR^{16}, CH_2R^{16}, COR^{17}, CO_2R^{17}, $CONR^{17}R^{17}$, SOR^{17} and SO_2R^{17} and wherein the alkyl, haloalkyl and heteroalkyl are optionally substituted;

R^{16} is selected from the group of hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl., C_1-C_8 heteroalkyl, COR^{17}, CO_2R^{17} and $CONR^{17}R^{17}$ and wherein the alkyl, heteroalkyl, and haloalkyl groups are optionally substituted;

R^{17} is selected from the group of hydrogen, C_1-C_4 alkyl, C_1-C_4 haloalkyl and C_1-C_4 heteroalkyl and wherein the alkyl, haloalkyl and heteroalkyl groups are optionally substituted;

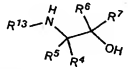
m is 0, 1, or 2;

Y is O or S;

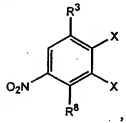
Z is selected from the group of O, $S(O)_m$, NH, NR^{11}, $NC(Y)R^{11}$, NSO_2R^{12} or $NS(O)R^{12}$;

that comprises the steps of:

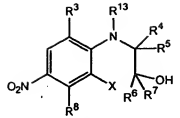
(a) treating either a single enantiomer, diastereomers, or the racemate of a secondary aminoalcohol of the formula



with a 3,4-dihalonitrobenzene of the formula

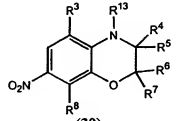


where X is fluorine or chlorine, to afford tertiary aminoalcohol 42



(42); and

(b) treating tertiary aminoalcohol **42** with a base to form the 3,4-dihydro-7-nitro-2*H*-1,4-benzoxazine intermediate **39**



(39)

as either a single enantiomer, diastereomers, or the racemate.

INTERNATIONAL SEARCH REPORT

Int Ional Application No
PCT/US 00/23520

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D498/04 C07D471/04 C07D513/04 A61K31/538 A61K31/5415 A61K31/502 A61P5/26 A61P5/28 //(C07D498/04,265:00, 221:00),(C07D471/04,241:00,221:00),(C07D513/04,279:00,221:00),

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 696 130 A (HAMANN LAWRENCE G ET AL) 9 December 1997 (1997-12-09) cited in the application abstract; claims 1,6,7 ---	1
X	WO 97 49709 A (EDWARDS JAMES P ;HIGUCHI ROBERT (US); JONES TODD (US); LIGAND PHAR) 31 December 1997 (1997-12-31) cited in the application abstract; claims 1,2,6,7 ---	1
X	EP 0 542 609 A (ADIR) 19 May 1993 (1993-05-19) page 14; claim 1; example 8 --- -/--	1

[X] Further documents are listed in the continuation of box C.

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& document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 February 2001	12/02/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 (C07D498/04,265:00,221:00),(C07D498/04,265:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 97 00876 A (SOD CONSEILS RECH APPLIC ;BIGG DENNIS (FR); LAVERGNE OLIVIER (FR);) 9 January 1997 (1997-01-09) claim 2; figure II	1
X	WO 95 24394 A (TAKEDA CHEMICAL INDUSTRIES LTD ;SOHDA TAKASHI (JP); MAKINO HARUHIK) 14 September 1995 (1995-09-14) page 66; claim 1; examples 9,10	1
X	PATENT ABSTRACTS OF JAPAN vol. 009, no. 188 (C-295), 3 August 1985 (1985-08-03) -& JP 60 056985 A (SANKYO KK), 2 April 1985 (1985-04-02) abstract page 10, column 2; table	1

-/--

[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the International search	Date of mailing of the international search report
1 February 2001	

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Paisdor, B

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2 058 788 A (SQUIBB & SONS INC) 15 April 1981 (1981-04-15) page 2 -page 4; claims	1
X	PATENT ABSTRACTS OF JAPAN vol. 004, no. 019 (C-073), 16 February 1980 (1980-02-16) -& JP 54 154797 A (EISAI CO LTD), 6 December 1979 (1979-12-06) abstract page 3, column 2; examples IV,V	1
X	DE 26 11 824 A (ICI LTD) 30 September 1976 (1976-09-30) page 30; examples 12,13 column 32; examples 45,54	1
X	US 3 936 461 A (SCHWENDER CHARLES F ET AL) 3 February 1976 (1976-02-03) column 25; example 53	1
X	US 3 755 332 A (WASLEY J ET AL) 28 August 1973 (1973-08-28) column 5 -column 6; tables	1
X	DE 21 11 938 A (F. HOFFMANN-LA ROCHE & CO. AG) 7 October 1971 (1971-10-07) page 39 -page 40; example 20 page 38	1
X	US 4 138 490 A (BRITTAIN DAVID R ET AL) 6 February 1979 (1979-02-06) abstract column 15; examples 12,13,45,54 column 19; example 71	1
P,X	WO 00 66680 A (URAY GEORG ;NIEDERREITER KARLHEINZ (AT)) 9 November 2000 (2000-11-09) page 8; example 1 claim 1	1
P,X	PATENT ABSTRACTS OF JAPAN vol. 1999, no. 14, 22 December 1999 (1999-12-22) -& JP 11 242304 A (KONICA CORP), 7 September 1999 (1999-09-07) abstract page 16; examples 5-7	1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int ional Application No
PCT/US 00/23520

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5696130 A	09-12-1997	AU 717251 B	23-03-2000
		AU 4597796 A	10-07-1996
		BR 9510486 A	02-06-1998
		CA 2208347 A	27-06-1996
		CN 1175247 A	04-03-1998
		CZ 9701761 A	16-09-1998
		EP 1043325 A	11-10-2000
		EP 1043326 A	11-10-2000
		EP 1041071 A	04-10-2000
		EP 1041066 A	04-10-2000
		EP 1043315 A	11-10-2000
		EP 0800519 A	15-10-1997
		HU 78117 A	29-11-1999
		JP 10510840 T	20-10-1998
		NO 972591 A	14-08-1997
		WO 9619458 A	27-06-1996
		US 6121450 A	19-09-2000
		NO 20003550 A	14-08-1997
		NO 20003551 A	14-08-1997
		NO 20003552 A	14-08-1997
		US 5688808 A	18-11-1997
		US 5693646 A	02-12-1997
		US 5688810 A	18-11-1997
		US 5693647 A	02-12-1997
		US 5696127 A	09-12-1997
		US 5696133 A	09-12-1997
		US 6093821 A	25-07-2000
		US 5994544 A	30-11-1999
WO 9749709 A	31-12-1997	AU 3508497 A	14-01-1998
		CA 2259031 A	31-12-1997
		EP 0918774 A	02-06-1999
		JP 2000513362 T	10-10-2000
		NO 986100 A	23-12-1998
		US 6017924 A	25-01-2000
EP 0542609 A	19-05-1993	FR 2683818 A	21-05-1993
		AT 111082 T	15-09-1994
		AU 651255 B	14-07-1994
		AU 2835192 A	20-05-1993
		CA 2082856 A	15-05-1993
		DE 69200394 D	13-10-1994
		DE 69200394 T	27-04-1995
		DK 542609 T	20-03-1995
		ES 2064156 T	16-01-1995
		JP 1969700 C	18-09-1995
		JP 5221997 A	31-08-1993
		JP 6102650 B	14-12-1994
		NZ 245127 A	26-07-1994
		ZA 9208727 A	10-05-1993
WO 9700876 A	09-01-1997	AU 716377 B	24-02-2000
		AU 6460896 A	22-01-1997
		BR 9608639 A	29-06-1999
		CA 2225528 A	09-01-1997
		CN 1192740 A	09-09-1998
		CZ 9704153 A	12-08-1998
		EP 0835258 A	15-04-1998

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9700876 A		JP 11508249 T	21-07-1999
		NO 975988 A	19-02-1998
		PL 324339 A	25-05-1998
		US 5981542 A	09-11-1999
		ZA 9605318 A	24-01-1997
WO 9524394 A	14-09-1995	AU 1860995 A	25-09-1995
		CA 2184392 A	14-09-1995
		EP 0749426 A	27-12-1996
		JP 8225531 A	03-09-1996
		US 5650410 A	22-07-1997
JP 60056985 A	02-04-1985	JP 1740386 C	15-03-1993
		JP 4027987 B	13-05-1992
GB 2058788 A	15-04-1981	US 4234589 A	18-11-1980
		DE 3036039 A	09-04-1981
		FR 2465733 A	27-03-1981
		JP 56055391 A	15-05-1981
JP 54154797 A	06-12-1979	NONE	
DE 2611824 A	30-09-1976	GB 1502312 A	01-03-1978
		AU 1147676 A	01-09-1977
		BE 839839 A	20-09-1976
		CS 188273 B	28-02-1979
		DD 124117 A	02-02-1977
		DK 115376 A	21-09-1976
		ES 446234 A	01-10-1977
		ES 459382 A	16-11-1978
		FI 760729 A	21-09-1976
		FR 2304342 A	15-10-1976
		HU 172032 B	28-05-1978
		IE 43079 B	17-12-1980
		JP 1022267 B	25-04-1989
		JP 1538991 C	16-01-1990
		JP 51118773 A	18-10-1976
		LU 74594 A	06-05-1977
		NL 7602834 A	22-09-1976
		NO 760993 A	21-09-1976
		PT 64921 A,B	01-04-1976
		SE 434394 B	23-07-1984
		SE 7602339 A	21-09-1976
		SU 648090 A	15-02-1979
		US 4066651 A	03-01-1978
		US 4138490 A	06-02-1979
		US 4187310 A	05-02-1980
		ZA 7601097 A	23-02-1977
		AT 350574 B	11-06-1979
		AT 776777 A	15-11-1978
US 3936461 A	03-02-1976	NONE	
US 3755332 A	28-08-1973	NONE	
DE 2111938 A	07-10-1971	AT 341116 B	25-01-1978
		AT 220971 A	15-05-1977
		BE 764252 A	15-09-1971

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE 2111938 A		CA 940530 A	22-01-1974
		CH 590274 A	29-07-1977
		CH 590275 A	29-07-1977
		DK 136983 B	27-12-1977
		DK 137189 B	30-01-1978
		DK 232876 A	26-05-1976
		FR 2100618 A	24-03-1972
		GB 1313963 A	18-04-1973
		IE 35284 B	07-01-1976
		IL 36400 A	30-07-1973
		NL 7103506 A	20-09-1971
		PH 9976 A	16-06-1976
		PH 9794 A	17-03-1976
		SE 395699 B	22-08-1977
		ZA 7101588 A	29-12-1971
US 4138490 A	06-02-1979	GB 1502312 A	01-03-1978
		AU 1147676 A	01-09-1977
		BE 839839 A	20-09-1976
		CS 188273 B	28-02-1979
		DD 124117 A	02-02-1977
		DE 2611824 A	30-09-1976
		DK 115376 A	21-09-1976
		ES 446234 A	01-10-1977
		ES 459382 A	16-11-1978
		FI 760729 A	21-09-1976
		FR 2304342 A	15-10-1976
		HU 172032 B	28-05-1978
		IE 43079 B	17-12-1980
		JP 1022267 B	25-04-1989
		JP 1538991 C	16-01-1990
		JP 51118773 A	18-10-1976
		LU 74594 A	06-05-1977
		NL 7602834 A	22-09-1976
		NO 760993 A	21-09-1976
		PT 64921 A,B	01-04-1976
		SE 434394 B	23-07-1984
		SE 7602339 A	21-09-1976
		SU 648090 A	15-02-1979
		US 4066651 A	03-01-1978
		US 4187310 A	05-02-1980
		ZA 7601097 A	23-02-1977
		AT 350574 B	11-06-1979
		AT 776777 A	15-11-1978
WO 0066680 A	09-11-2000	AT 77599 A	15-11-2000
JP 11242304 A	07-09-1999	NONE	